CHEMICAL INVESTIGATION IN THE CHOLESTANE SERIES

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This is to certify that the work described in this thesis is the original work of the candidate done under my supervision. The thesis is suitable for submission for the award of Ph.D. degree in Chemistry.

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(M.S. AHMAD)
Professor of Chemistry

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(NAJAM ZAHIR KHAN)

CONTENTS

SUMMARY

PART - I.

Previous work from these laboratories has described the preparation of several steroidal cyclic acetals from the respective ketones and the lithium aluminium hydride-aluminium chloride (1:1, AlH_2Cl) reduction of the former in to the corresponding hydroxyethers. The present study was undertaken in order:

(a) to extend the lithium aluminium hydride-aluminium chloride reduction to other unexplored, yet easily accessible steroidal cyclic acetals, especially those derived from steroidal diones,

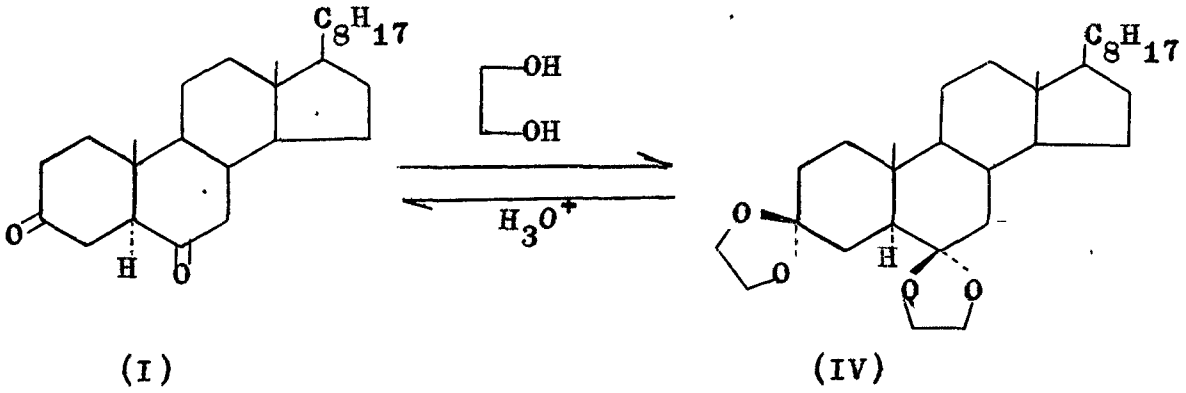
(b) to study the effect of C4-C5 double bond on the hydrogenolysis of steroidal bisacetals of 3,6-diones,

(c) to evaluate the synthetic utility of these reactions in steroidal systems and,

(d) to check the validity of the generally accepted mechanism of hydrogenolysis of steroidal cyclic acetals.

For the present study 5α-cholestane-3,6-dione (I), cholest-4-ene-3,6-dione (II), and 5-hydroxy-5α-cholestane-3,6-dione (III) were selected. The structure of the products concerned have been established by chemical and spectral methods. The results have been summarized in the following flow sheets.

Preparation and $LiAlH_4$-$AlCl_3$ reduction of 3,3,6,6-bis-ethylenedioxy-5α-cholestane (IV).



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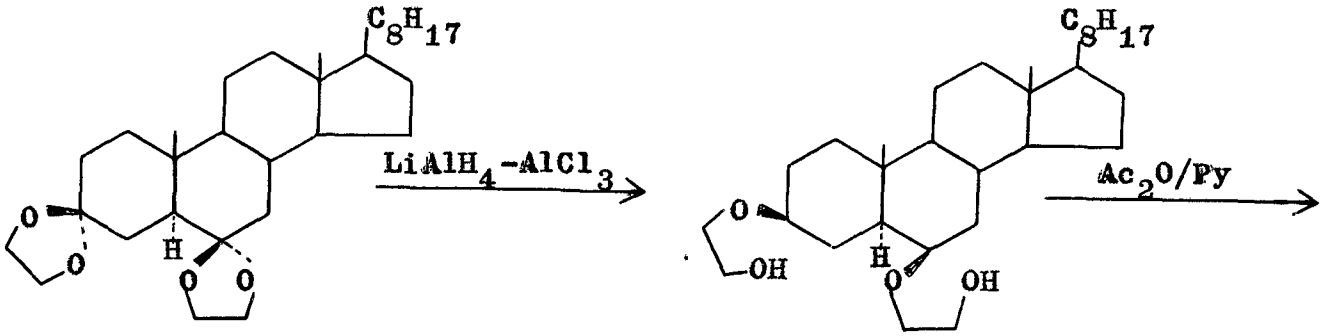

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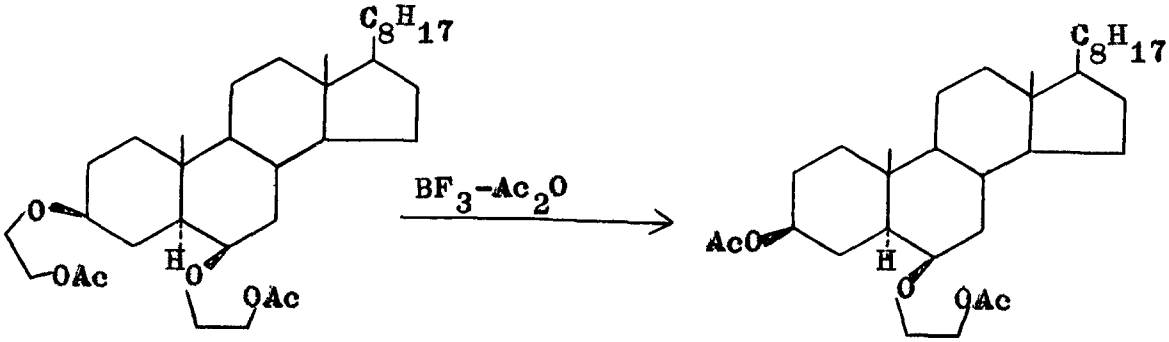
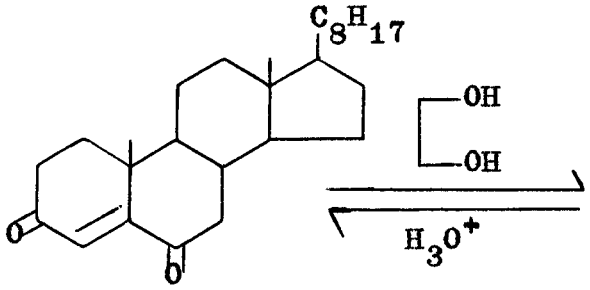


(VI) (VII)

Preparation and $LiAlH_4$-$AlCl_3$ reduction of 3,3,6,6-bis-ethylenedioxycholest-4-ene (VIII).



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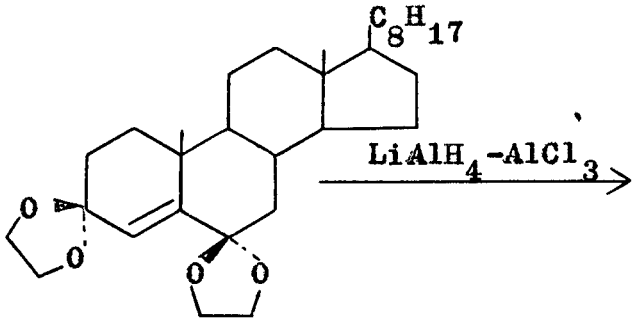

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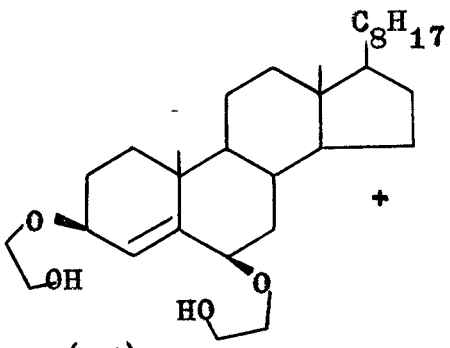

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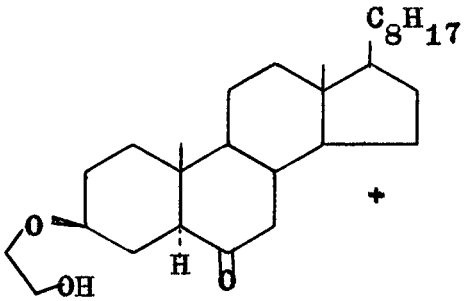
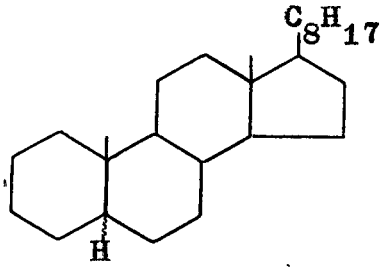


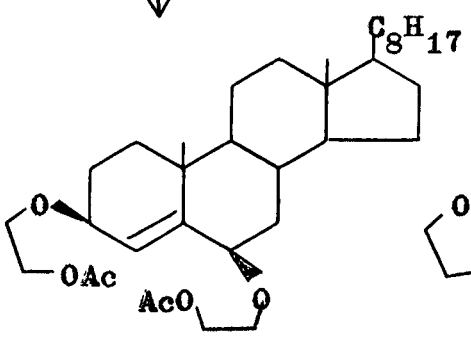
(X)



(XI)

Ac_2O/Py

Ac_2O/Py



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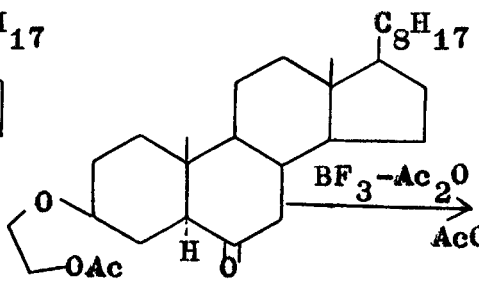

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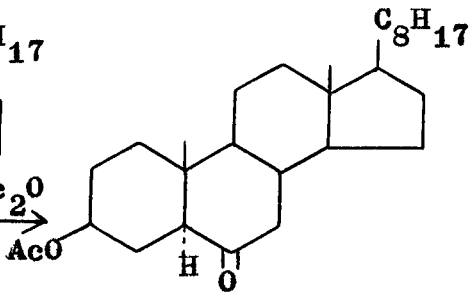
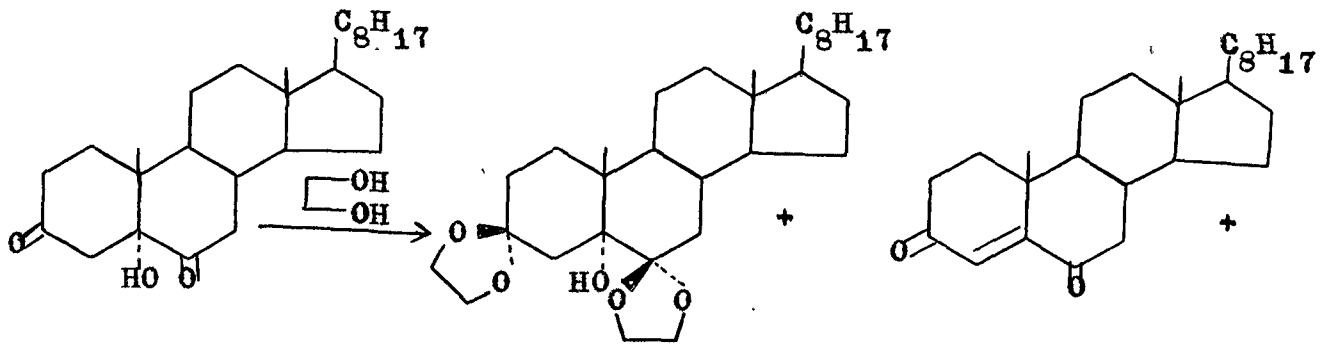


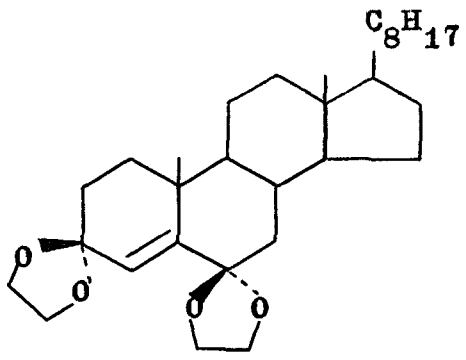
(XIV)

A probable mechanism has been proposed which accounts for the formation of the saturated hydrocarbon/s (XI) and (X), besides the normal hydroxyether (IX).

Preparation of 5-hydroxy-3,3,6,6-bisethylenedioxy-5α-cholestane (XV).



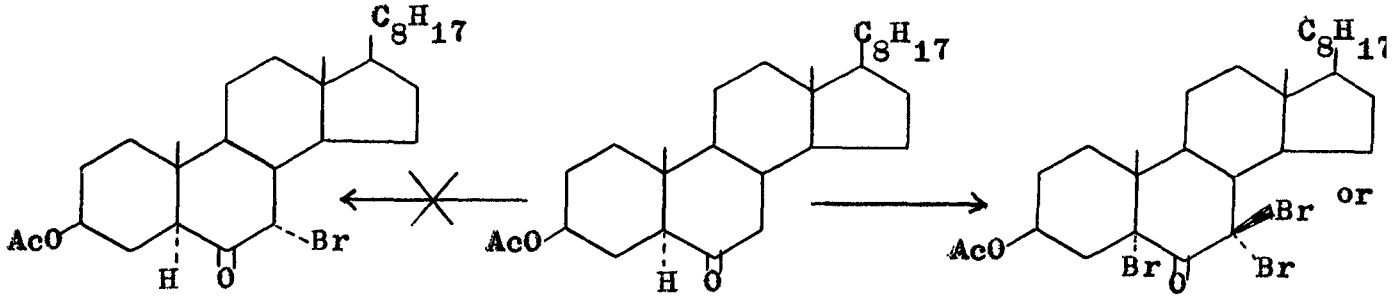
(III) (XV) (II)



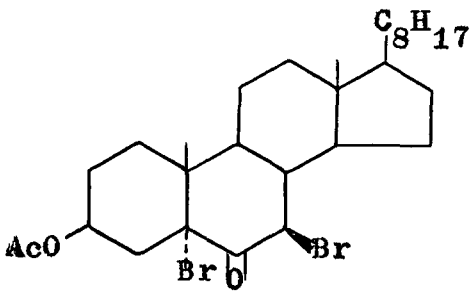
(VIII)

PART - II.

In an attempted preparation of 3β-acetoxy-7α-bromo-5α-cholestan-6-one (XVI), 3β-acetoxy-5α-cholestan-6-one (XIV) was treated with Br_2-HBr in ether-acetic acid. This invariably afforded a product, m.p. 186°, after column chromatography and crystallization, which was characterised as 3β-acetoxy-5,7,7-tribromo-5α-cholestan-6-one (XVII) on the basis of spectral and chemical studies. In one or two experiments, under similar conditions, a product, m.p. 140° was obtained which was identified as 3β-acetoxy-5,7β-dibromo-5α-cholestan-6-one (XVIII). None of these products was found to be the desired 7α-bromo-ketone (XVI).

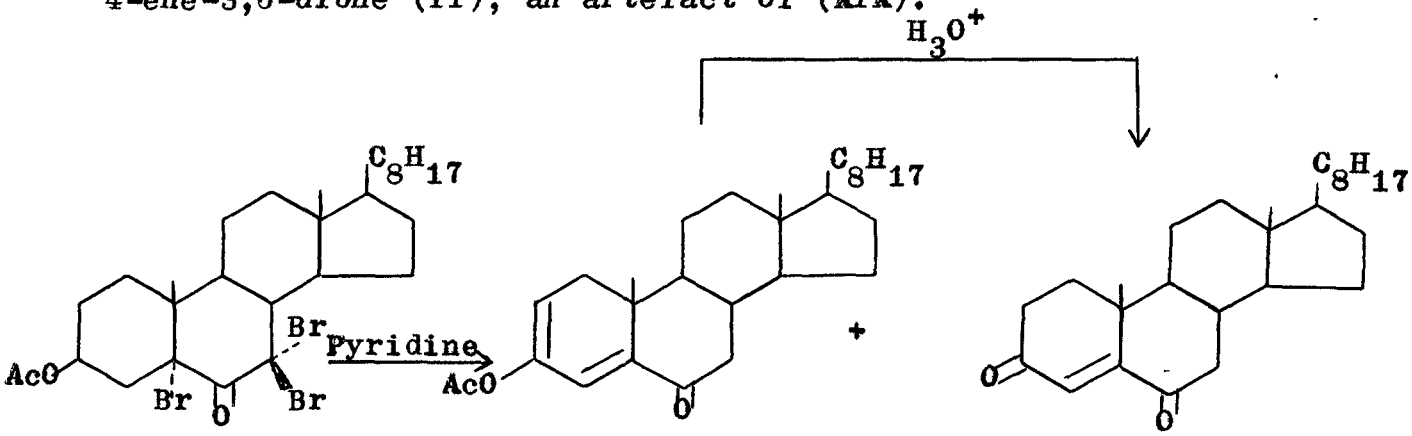


(XVI) (XIV) (XVII)

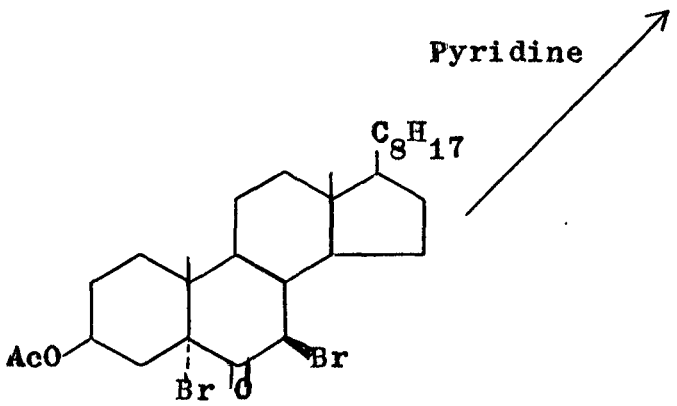


(XVIII)

Interestingly both the tribromo-ketone (XVII) and the dibromo-ketone (XVIII) with refluxing pyridine gave the same products, 3-acetoxycholesta-2,4-dien-6-one (XIX) and cholest-4-ene-3,6-dione (II); an artefact of (XIX).



(XVII) (XIX) (II)

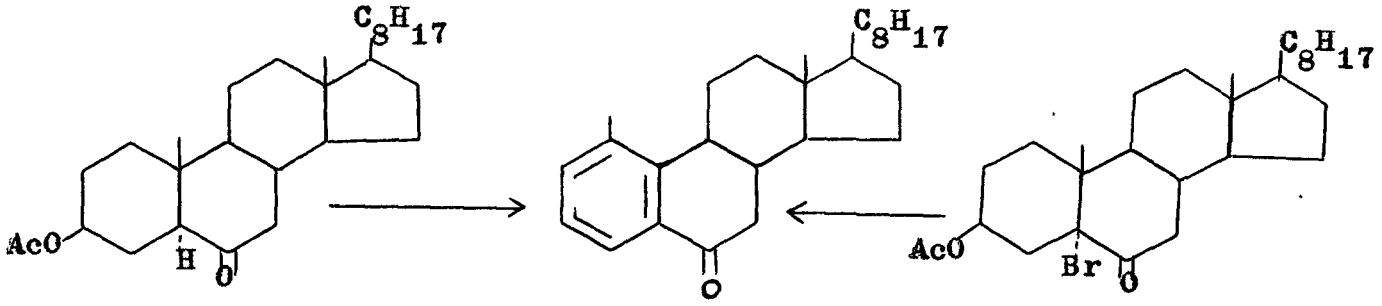


(XVIII)

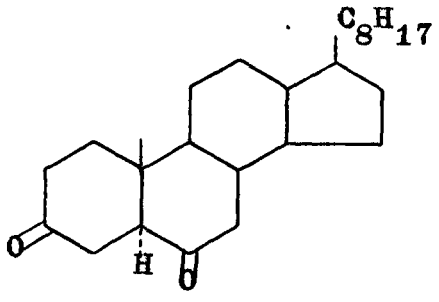
A probable mechanism for the formation of 3-acetoxycholesta-2,4-dien-6-one (XIX) from 3β-acetoxy,5,7,7-tribromo-5α-cholestan-6-one (XVII) has been proposed. The conversion (XVII) → (XIX) requires that α-debromination should occur at one stage or the other during the course of the reaction.

Mass spectra of the dehydrobrominated products (XIX) and (II) have been considered in some details.

In our continued efforts to prepare 3β-acetoxy-7α-bromo-5α-cholestan-6-one (XVI) from (XIV), the latter was heated with Br_2/HBr in ether-acetic acid for 22 hours. This provided the product of ring A aromatization, 1-methylcholesta-1,3,5(10)-trien-6-one (XX) and 5α-cholestan-3,6-dione (I).



(XIV) (XX)

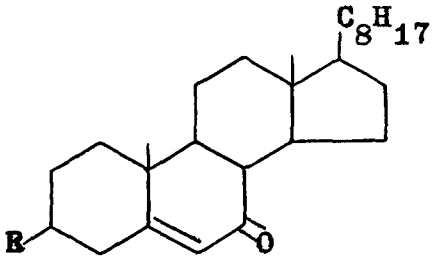


(I)

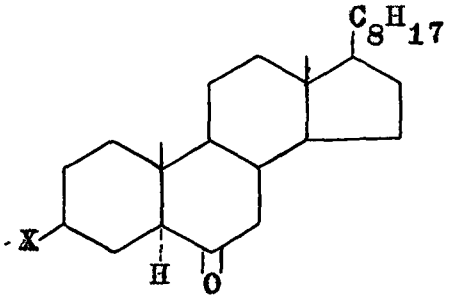
A tentative mechanism has been proposed to account for the above mentioned observations.

PART - III.

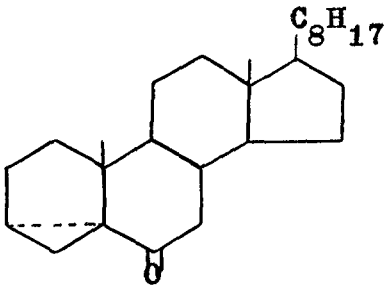
Previous work from these laboratories described the perbenzoic acid oxidation of 3β-acetoxycholest-5-en-7-one (XXI), cholest-5-en-7-one (XXII), 3β-halo-5α-cholestan-6-ones (XXIII), (XXIV) and (XXV), 3α,5-cyclo-5α-cholestan-6-one (XXVI) and 6β-bromocholest-4-ên-3-one (XXVII).



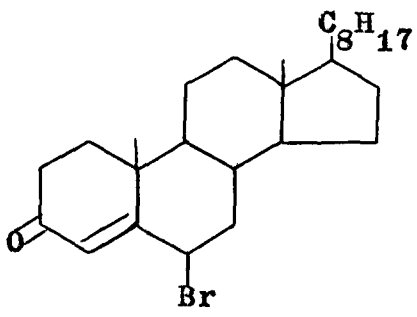
(XXI) R, AcO
(XXII) R, H



(XXIII) X, Cl
(XXIV) X, Br
(XXV) X, I

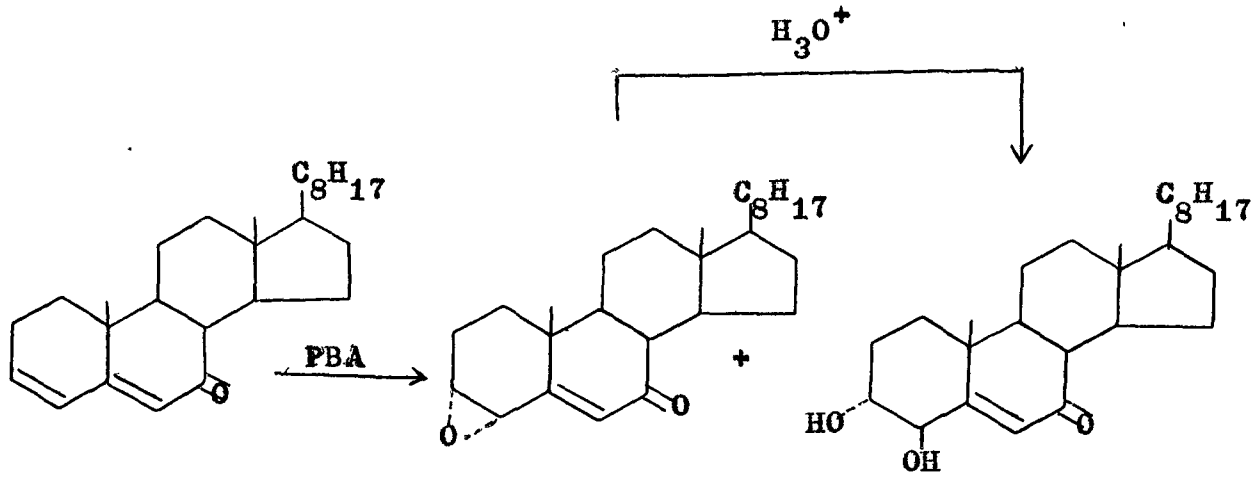


(XXVI)

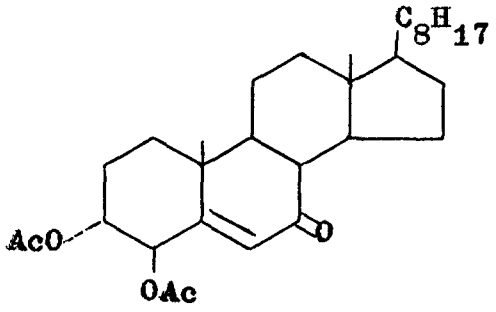


(XXVII)

In anticipation of obtaining some interesting results and to extend the above work cholesta-3,5-dien-7-one (XXVIII) was subjected to Baeyer-Villiger oxidation conditions. With per-benzoic acid (XXVIII) gave the epoxy-ketone, 3α,4α-epoxycholest-5-en-7-one (XXIX) and its artefact, 3α,4β-dihydroxycholest-5-en-7-one (XXX) and no expected lactone was obtained.

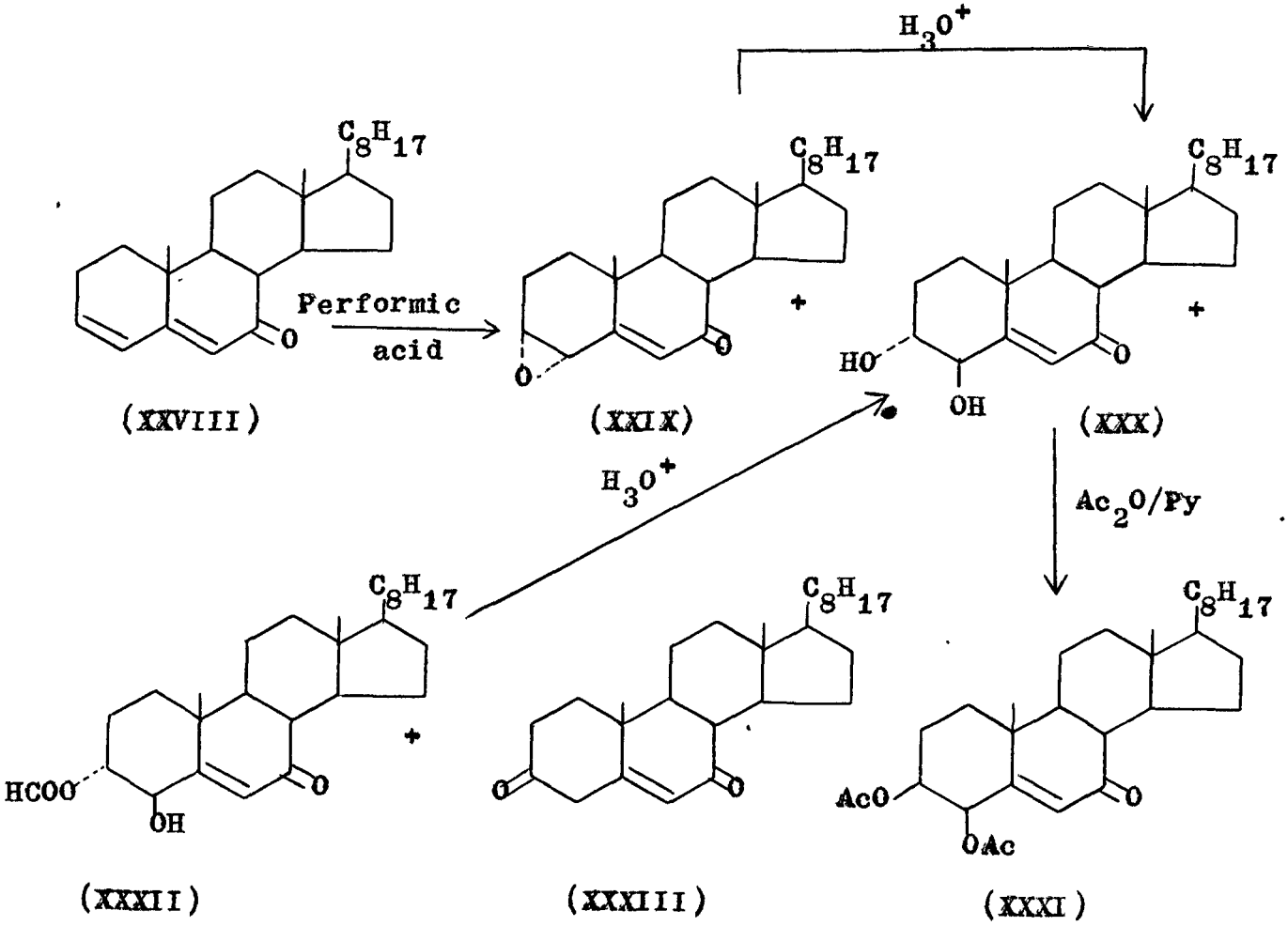


(XXVIII) (XXIX) (XXX)



(XXXI)

In order to obtain the corresponding lactone/s, the dienone (XXVIII) was treated with the varying quantities of performic acid for different lengths of time, Invariably, the reaction provided the epoxide (XXIX), the diol (XXX), 3α-formyloxy-4β-hydroxycholest-5-en-7-one (XXXII) and cholest-5-ene-3,7-dione (XXXIII); none of the expected ∈-lactone was obtained in this case also.



THEORETICAL

INTRODUCTION

A number of metal hydrides have been employed as reducing agents in organic chemistry, but the most commonly used are lithium aluminium hydride, $LiAlH_4$, and sodium borohydride, $NaBH_4$. Their frequent use has undoubtedly been related to their relative stability, ease of handling, accessibility and commercial availability.

Lithium aluminium hydride itself is an extremely powerful and versatile reducing agent. It is more reactive than sodium borohydride. It reacts readily with water and other compounds containing active hydrogen atoms, and must be used under anhydrous conditions in a non-hydroxylic solvent; ether and tetrahydrofuran are often employed. Sodium borohydride reacts only slowly with water or methanol at room temperature, and reductions with this reagent can be effected in methanol solution at room temperature.

Not long after the introduction of each of these reducing agents, chemists began to seek modifications to enhance their versatility and selectivity. These modifications have generally involved the addition of Lewis acids such as aluminium chloride and boron trifluoride to the complex metal hydrides. Such a

combination of Lewis acid and $LiAlH_4$ or $NaBH_4$ has come to be known as a 'mixed-hydride'.

In addition to the availability of the mixed hydrides, the versatility of $LiAlH_4$ and $NaBH_4$ has been modified by the development of the alkoxy substituted complex hydrides, $MAlH_n(OR)_{4-n}$ and $MBH_n(OR)_{4-n}$, as selective reducing agents. Add to this complement of reducing reagents diborane and aluminium hydride and the chemist has a wide array of boron and aluminium hydrides available for the reduction of organic functional groups.

Nature of the Mixed Hydrides.

A. Lithium Aluminium Hydride and Aluminium Halides:

A very useful modification of the properties of lithium aluminium hydride is achieved by addition of aluminium chloride in various proportions. This serves to release various mixed chloride-hydrides of aluminium and those prepared from hydride and chloride in ratios of 3:1, 1:1, 1:3 and 1:4 have been utilized for reduction most frequently. The first three of these ratios correspond to the stoichiometric ratios in equations (1-3).

$$3\ LiAlH_4 + AlCl_3 \longrightarrow 3\ LiCl + 3\ AlH_3 \quad ----- (1)$$

$$LiAlH_4 + AlCl_3 \longrightarrow LiCl + 2\ AlH_2Cl \quad ----- (2)$$

$$LiAlH_4 + 3\ AlCl_3 \longrightarrow LiCl + 4\ AlHCl_2 \quad ----- (3)$$

The general effect of the addition of aluminium chloride is to lower the reducing power of lithium aluminium hydride and in consequence to produce reagents which are more specific for particular reactions. The formation of aluminium hydride in equation (1), has been demonstrated by Schlesinger et al .[1] and Wiberg et al.[2] If the reaction is carried out in diethyl ether, the precipitated lithium chloride may be removed by filtration. Unfortunately, a rapid polymerisation[1,2] of aluminium hydride ensues, and within minutes of mixing the reagents, the polymer begins to precipitate from solution.

$$n\ AlH_3 \longrightarrow (AlH_3)_n\downarrow \quad \text{- - - - - - - - - - (4)}$$

The monomeric species may be stabilised in solution by addition of tetrahydrofuran (THF)[3].

$$(AlH_3)_n + n\ THF \longrightarrow n\ AlH_3\text{-}THF \quad \text{- - - - - - (5)}$$

A direct preparation of aluminium hydride in THF from $LiAlH_4$ and 100% sulphuric acid has been described by Brown and Yoon[4].

$$2LiAlH_4 + H_2SO_4 \xrightarrow{THF} Li_2SO_4 + 2\ AlH_3 + 2H_2 \quad \text{- - - (6)}$$

The ethereal aluminium hydride may also be stabilized by the addition of 1 mole of aluminium chloride with the production of $Al_2H_3Cl_3$ [5,6].

$$AlH_3 + AlCl_3 \longrightarrow Al_2H_3Cl_3 \quad \text{- - - - - - - - - - (7)}$$

Addition of two moles of aluminium chloride proceeds with the formation of aluminium dichlorohydride[6],

$$AlH_3 + 2AlCl_3 \longrightarrow 3AlHCl_2 \quad \text{- - - - - - - - - - - (8)}$$

whereas addition of 1/2 mole of aluminium chloride leads to the formation of polymeric aluminium hydride and $Al_2H_3Cl_3$, rather than the "unstable" AlH_2Cl[6].

$$2AlH_3 + AlCl_3 \not\longrightarrow 3AlH_2Cl \quad \text{- - - - - - - - - (9)}$$

$$2AlH_3 + AlCl_3 \longrightarrow (AlH_3)_n + Al_2H_3Cl_3 \quad \text{- - -(10)}$$

Ashby and Prather[7] have provided convincing evidence for the stoichiometry shown in Eq. (1) and conclusive evidence for the formation of the aluminium chlorohydrides as shown in Eqns. (2) and (3). Each of the hydride was isolated and each was identified by elemental analysis and by formation of triethylaminates $AlH_nCl_{3-n}N(CH_2CH_3)_3$. These authors suggest that as the hydride is added to the aluminium chloride, $AlHCl_2$ is first formed. As the amount of $LiAlH_4$ is increased, $AlHCl_2$ disappears and AlH_2Cl is formed. Ultimately, at a hydride chloride ratio of 3:1, AlH_3 is formed.

$$AlCl_3 \longrightarrow AlHCl_2 \rightleftharpoons AlH_2Cl \rightleftharpoons AlH_3 \quad \text{- - - - - - (11)}$$

Brown and coworkers[8] have shown that these species do in fact exist in ethereal solution and that the conversion of aluminium chloride to aluminium hydride occurs as shown in Eq.(11).

Furthermore, they have demonstrated that the conversions are reversible; i.e., aluminium hydride may be converted to aluminium-chlorohydrides by the addition of aluminium chloride.

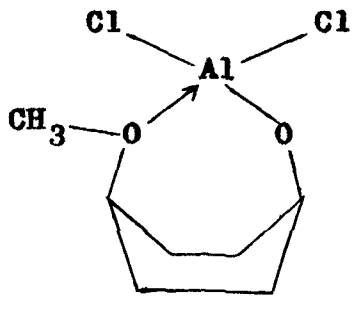
Ashby and Prather[7] also suggest that the reason for the rather startling failure of the ether insoluble lithium chloride to precipitate, Eqns. (2) and (3), at low hydride-halide ratios is due to complex formation between lithium chloride and aluminium chlorohydrides.

In many reductions particularly in those studied by Eliel and coworkers[9], the ratio of hydride to chloride is 1:4. Ashby and Prather[7] have confirmed the earlier assumption that this reagent, and those of lower ratios of hydride to chloride, merely contains aluminium dichlorohydride and excess of aluminium chloride,

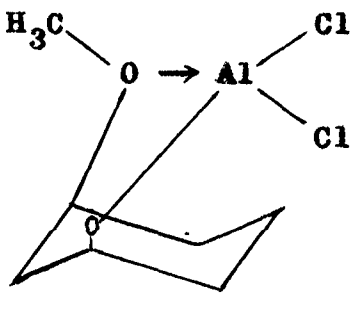
$$LiAlH_4 + 4AlCl_3 \longrightarrow LiCl + 4AlHCl_2 + AlCl_3 \quad - - - - - - - (12)$$

the soluble lithium chloride being complexed with either the $AlHCl_2$ or $AlCl_3$.

Eliel and Brett[10] had earlier reported some evidence indicative of $AlHCl_2$ as the product of equation (5). Treatment of a mixture of cis- and trans-4-methoxycyclohexanol with the mixed hydride prepared from $LiAlH_4$ with $AlCl_3$ (1:4 mole ratio) gave only the cis- chelate (I).



(I)



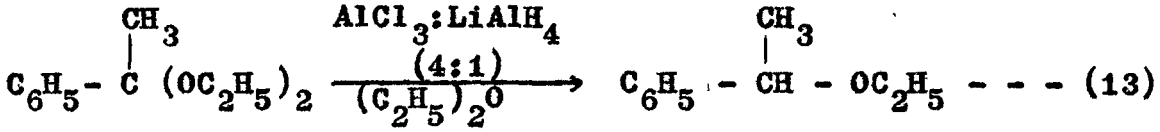
(II)

Similar treatment of cis- and trans-3-methoxycyclohexanol gave only the cis-chelate (II). In each case the isolated chelate (and H_2) could have been formed by reactions of the alcohol and $AlHCl_2$.

Based on the work of Ashby and Prather[7], the stoichiometric equations (1-3) may be equally well applied to the mixed hydrides produced from $LiAlH_4$ and $AlBr_3$ or AlI_3. The etherates of $AlHBr_2$ and $AlHI_2$ have previously been described by Wiberg and Schmidt[11,12] but were prepared by the redistribution of 1 mole of aluminium hydride and 2 moles of aluminium halide. Unlike AlH_2Cl, AlH_2Br and AlH_2I could be prepared by redistribution of 2 moles of aluminium hydride and 1 mole of aluminium halide.

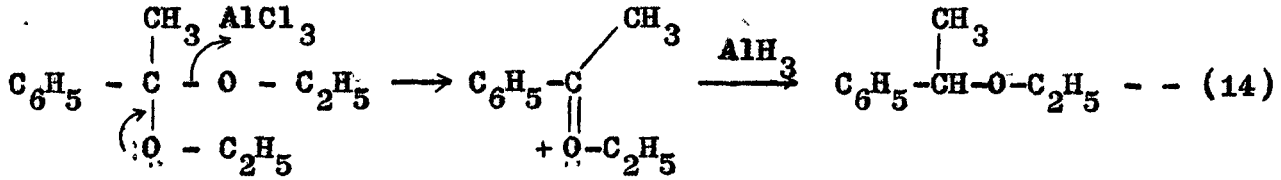
There would seem to be little doubt as to the nature of these mixed hydrides. However, a somewhat perplexing contradiction does exist. Evans and coworkers have studied the conductometric titration of $LiAlH_4$ with aluminium chloride[13] and aluminium iodide[14] and have concluded that ionic species intervene in the formation of both AlH_2Cl and AlH_2I. Their evidence also indicates that $AlHCl_2$ and $AlHI_2$ are 'not' intermediates in the formation of AlH_2Cl and AlH_2I. Evans' data have been verified by Arkhipov and Mukheeva[15] and this procedure extended to aluminium bromide[16]. A rationale of the intervention of the ionic species has not been offered[7].

The mixed aluminium chloride-lithium aluminium hydride reagent has also found use for the reduction of ketals and acetals[17], as illustrated in the accompanying equation (13). For these reductions, the best yields were obtained when an $AlCl_3$:$LiAlH_4$ ratio of 4:1 was employed.



$$C_6H_5-\overset{CH_3}{\underset{|}{C}}(OC_2H_5)_2 \xrightarrow[(C_2H_5)_2O]{AlCl_3:LiAlH_4\ (4:1)} C_6H_5-\overset{CH_3}{\underset{|}{CH}}-OC_2H_5 \quad ---(13)$$

It seems probable that the excess Lewis acid serves to cleave the acetal to an oxonium ion, Eqn. (14), which is then reduced by the aluminium hydride species present.



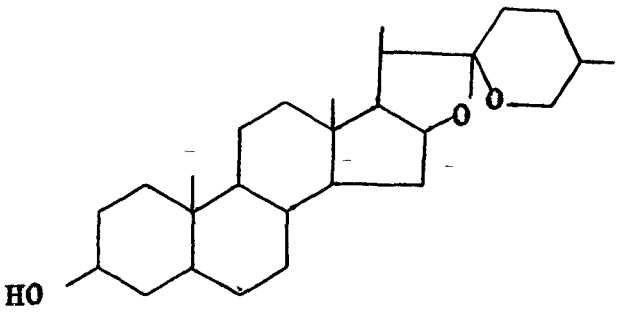
$$C_6H_5-\overset{CH_3}{\underset{|}{C}}(-O-AlCl_3)-O-C_2H_5 \longrightarrow C_6H_5-C(CH_3)=\overset{+}{O}-C_2H_5 \xrightarrow{AlH_3} C_6H_5-\overset{CH_3}{\underset{|}{CH}}-O-C_2H_5 \quad --(14)$$

Besides $AlCl_3$, the other reagents which can be used with $LiAlH_4$ to give 'mixed hydrides' are boron halides[1,18-20], metal salts[20-25], metal[23], pyridine[15,26-29], and alcohols[30,31]. These combinations have also been used with $NaBH_4$ to give "mixed hydride"[32-48].

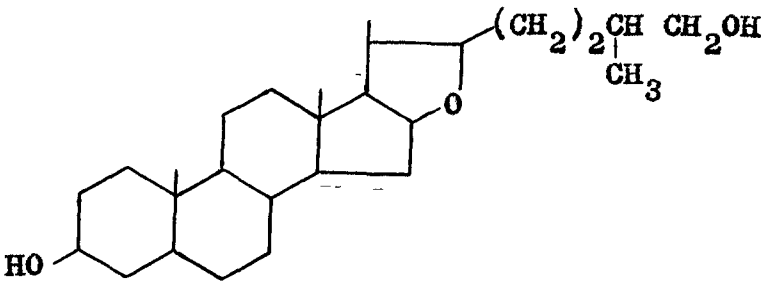
Hydrogenolysis of Acetals with Mixed Hydrides:

In 1951, Doukas and Fontaine[49] reported that spirostanes such as (III) are reduced to furostanols, such as (IV), by the addition of solid lithium aluminium hydride to an ethereal

solution of the spirostane saturated with anhydrous hydrogen chloride or hydrogen bromide.



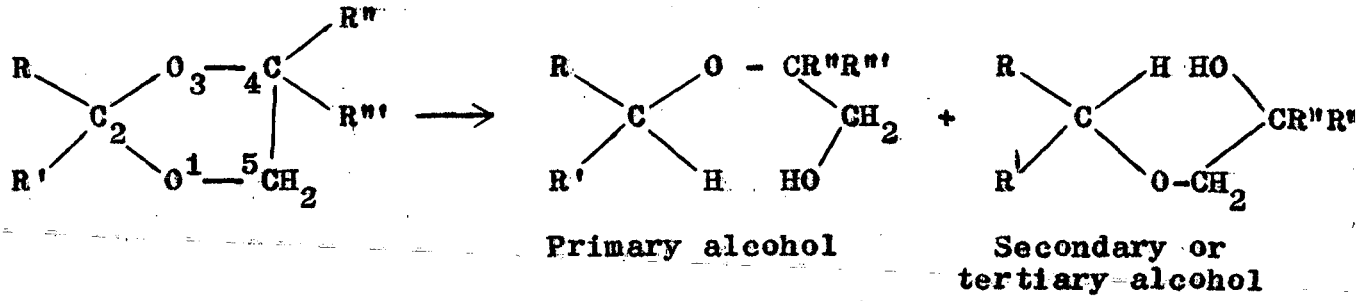
(III)



(IV)

This report was noteworthy for two reasons. The combination of reagents employed was rather unusual. (Neither $LiAlH_4$ nor hydrogen halides by themselves affected (III) and combinations of $LiAlH_4$ with hydrogen sulphide, sulphur dioxide and p-toluene-sulphonic acid were also ineffective). Also conversion of (III) to (IV) exemplifies reduction of an acetal to an ether for which no procedures giving acceptable yields were then available. In general, of course, the acetal function is resistant to the attack of $LiAlH_4$ and in fact, acetal formation often is employed to protect ketone groups during the reduction of other functions (such as ester groups) in a molecule[39]. Subsequent work disclosed that the reducing properties of $LiAlH_4$ may be considerably modified by addition of Lewis acids, especially aluminium chloride[50]. Eliel et al.[51,52] studied the action of such combination on a variety of acetals.

Leggetter and Brown[53] studied the hydrogenolysis of 1,3-dioxolanes by $LiAlH_4$-$AlCl_3$ at room temperature which can be represented by the following equation.



On the basis of experimental results, Leggetter and Brown arrived at a number of general conclusions[53].

1. The formyl acetals are hydrogenolysed with greater difficulty than are C_2 alkylated or arylated isomers and homologues.

2. A greater effect on the rate of reductive cleavage of dioxolane ring is exerted by substituents on position C_2 than by the same substituents on any other ring carbon atoms.

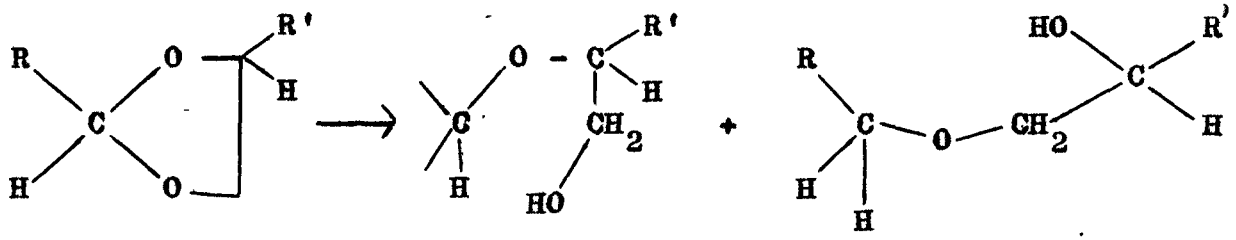
3. Electron-donating substituents (methyl, phenyl) accelerate while electron-withdrawing groups (chloromethyl, dichloromethyl) retard or prevent reductive cleavage of acetals. The effect is much more pronounced when these substituents are at C_2 than at any other carbon atom of the ring. The order of decreasing ability of the reductive cleavage of the dioxolanes when attached to the C_2 position of the ring is

$$C_6H_5- > (CH_3)_2- > CH_3- > H- > ClCH_2- > Cl_2CH-$$

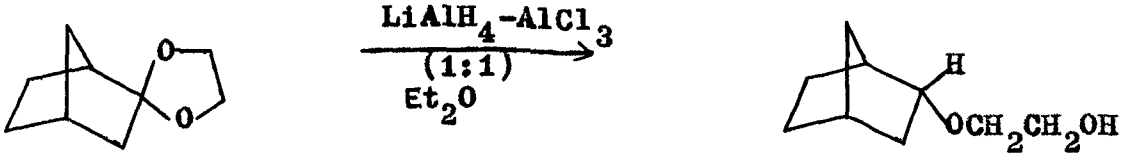
4. Electron-donor or acceptor attached to carbon atom C_4 or C_5 of the dioxolane ring exert marked control over the direction of ring cleavage. The results further show that by and large, substituents which by electron donation assist in the stabilization of the oxocarbonium ion will favour cleavage of the C2-O bond remote from the substituted carbon atom, thus yielding a high preponderance of the primary alcohol. The reverse effect due to an electron-withdrawing substituent is observed.

5. The final observation of interest concerning the data is that of the peculiar reduction experienced by 2-trichloromethyl-1, 3-dioxolane. The material recovered from this experiment, rather than being either the reduction product 2-β, β, β -trichloroethoxyethanol or the unchanged starting material, proved to be 2-dichloromethyl-1,3-dioxolane, which is stable to further reduction. Further work showed that the compound can be obtained by $LiAlH_4$ alone, although it is conceivable that aluminium chloride could in this case have been formed in situ during the course of the reaction. The formation can be explained on the analogous result found by Ruske and Hartman[54]. The basic character of lithium aluminium hydride could promote elimination of hydrogen chloride from the 2-trichloromethyl-1,3-dioxolane and the intermediate 2-dichloromethylene-1,3-dioxolane could then be reduced by the hydride.

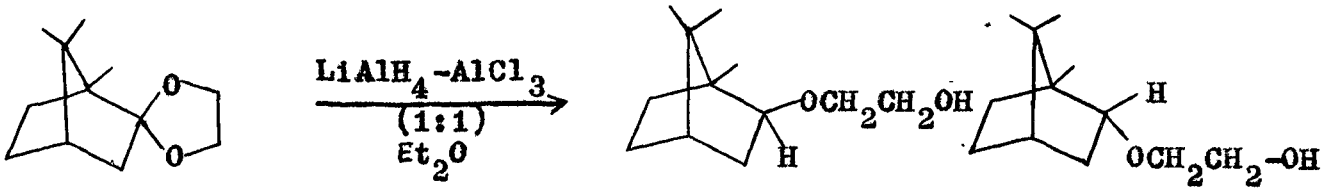
Hydrogenolysis of the cis and trans isomers of both 2,4-dimethyl-1,3-dioxolane and 2-ethyl-4-methyl-1,3-dioxolane has been carried out by Brown et al.[55] They showed that cis isomers are hydrogenolysed respectively, about 6,8 and 10 times faster than are the corresponding trans isomers. The ratio of C2-O1 to C2-O3 bond cleavage in the cis isomers is at least 15 to 1 while in the trans isomers is about 1 to 2. Isomerisation during the aluminium chloride catalysed hydrogenolysis is not deductable for the trans isomers. Slight indications of isomerisation are discerned for the cis isomers.



Hydrogenolysis of 1,3-dioxolanes of cyclic ketones has also been examined by Brown and coworkers[56,57]. Lithium aluminium hydride-aluminium chloride reductive cleavage of norcamphor ethylene acetal (V) gave 2-(2-endonorbornyloxy) ethanol (VI) in 98% yield whereas similar reduction of camphor ethylene acetal (VII) gave both 2-(2-isobornyloxy)ethanol (VIII) and 2-(2-bornyloxy) ethanol (IX) in 78% and 22% yields, respectively[56].



(V) (VI) 98%

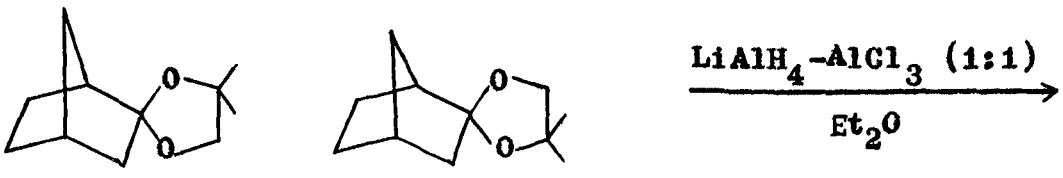


(VII) (VIII) 78% (IX) 22%

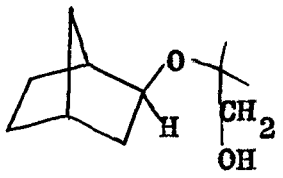
The hydrogenolysis of an inseparable mixture (1:1) of the two isomers (X) and (XI), of norcamphor isobutylene acetal was carried out using an equimolar mixture of $LiAlH_4$ and $AlCl_3$ in dry ethyl ether[57]. The results of hydrogenolysis are assembled in Table (I).

TABLE - I

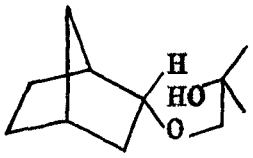
Time of reaction (mts)	Extent of reduction	Products of reaction, % of the total products (XIV)	(XIII)	(XII)	(X and XI)	Total recovery of the material %
20	62	2.5	42.5	17.0	38	95
168	95.5	4.5	64.5	26.5	4.5	95



(X) (XI)



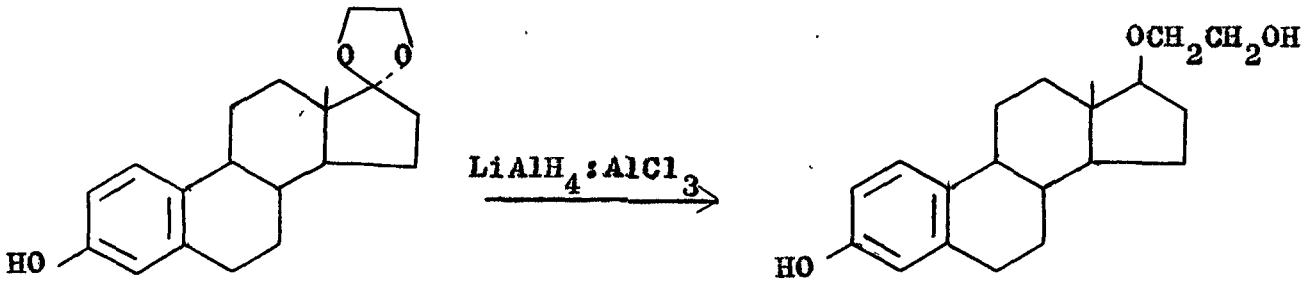
(XII)



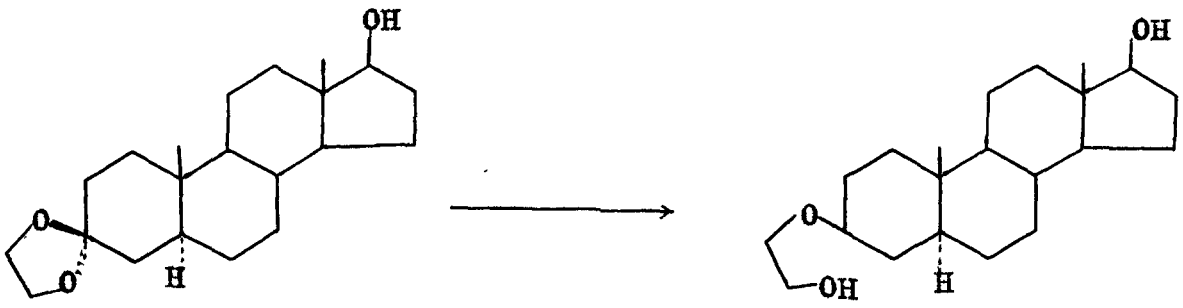
(XIII)

(XIV)

Studies on hydrogenolysis with mixed hydrides have also been extended to 1,3-dioxolanes of steroidal ketones in which the cleavage is stereospecific. Thus reduction of 17,17-ethylenedioxy-3-hydroxy-1,3,5(10)-estratriene (XV) with $LiAlH_4$-$AlCl_3$ (1:2) and reduction of 3,3-ethylenedioxy-17β-hydroxyandrostane (XVII) with aluminium hydride leads to the 17β-(2-hydroxyethoxy)- and 3β-(2-hydroxyethoxy)-, (XVI) and (XVIII) derivatives, respectively[58].

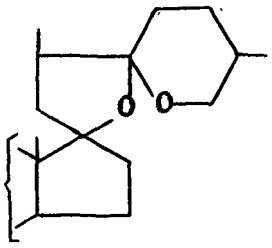


(XV) (XVI)

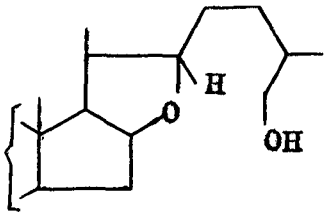


(XVII) (XVIII)

The system of acetals containing one oxygen in each of two different rings has been subjected to reduction with mixed hydrides. The opening of the sapogenin spiroacetal system (XIX) occurs, in all cases studied, such that the five membered ring remains intact to give (XX)[59].

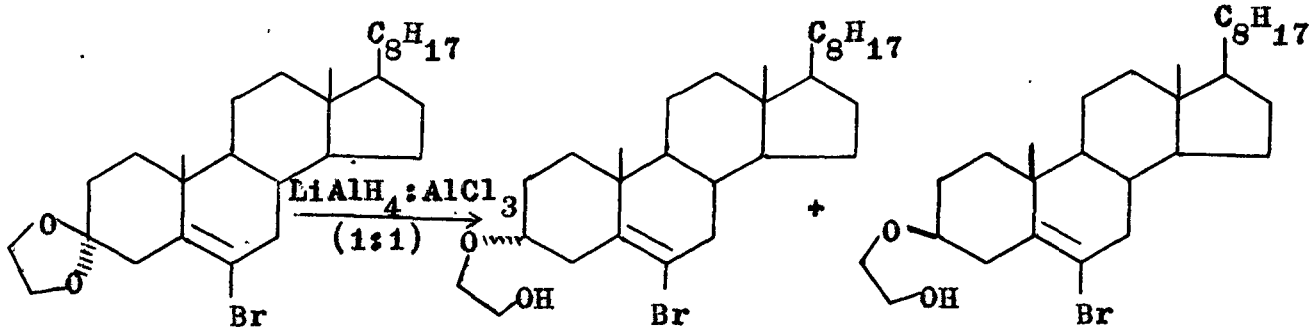


(XIX)



(XX)

Ahmad et al. have examined the lithium aluminium hydride-aluminium chloride (1:1) reduction of several easily accessible unexplored steroidal cyclic acetals. In each case studied they obtained only the β-epimer except in the case of 6-bromo-3,3-ethylenedioxycholest-5-ene (XXI) which on mixed hydride ($LiAlH_4$-$AlCl_3$, 1:1) reduction gave 6-bromo-3α-(2'-hydroxyethoxy)cholest-5-ene (XXII) and 6-bromo-3β-(2'-hydroxyethoxy)cholest-5-ene (XXIII) in the approximate ratio of 1:6, respectively[60].



(XXI) (XXII) (XXIII)

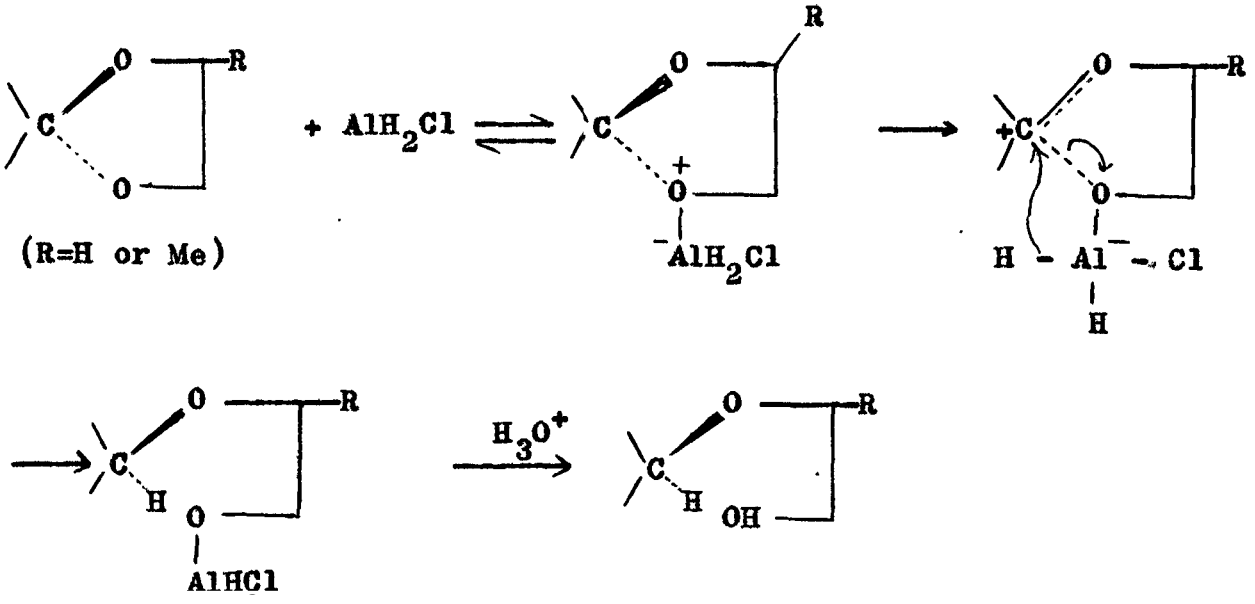
This difference in the behaviour of the acetal (XXI) may be explained on the basis of steric hinderance offered by the bromine atom at C6 to the incoming reducing species (AlH_2Cl) to the reaction site. The preferred course for the attack of AlH_2Cl on the acetal ring is from the rear-side, where the steric crowding is the least. The presence of bromine at C6 may offer steric hinderance to the incoming AlH_2Cl from the rear-side and therefore, a small amount of reactive species may also attack from the front side on β-oxygen to yield α-hydroxyether (XXII). The configurations of the ether moieties at their respective positions have been established through spectral data (n.m.r.) and their behaviour towards BF_3 etherate-acetic anhydride.

Mechanism of Hydrogenolysis of Acetals with Lithium Aluminium Hydride-Aluminium Chloride.

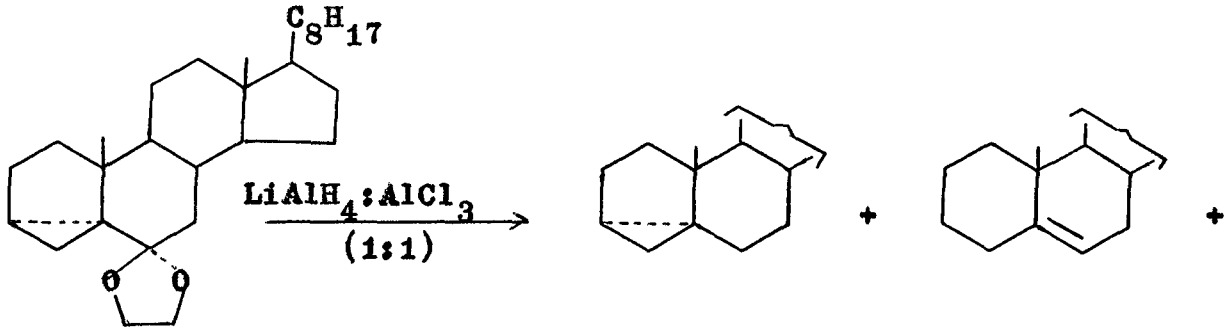
The study on lithium aluminium hydride-aluminium chloride reduction of steroidal cyclic acetals has shown that in each case

except one (XXI) only the β -epimer is obtained. The almost exclusive formation of β -oriented hydroxy ether can be explained if we assume that the first step in the reductive cleavage is the complexing of the aluminium species (AlH_2Cl) at the oxygen atom of the acetal ring from the less hindered α -side. Next step in the hydrogenolysis involves the cleavage of C-O bond in which the Lewis acid is associated with the oxygen atom and the migration of a hydride ion to the electrophilic carbon atom. The transfer of hydride ion to the electrophilic carbon can occur either from the same molecule of AlH_2Cl which is acting as the Lewis acid or from another molecule of AlH_2Cl. Since no α -epimer has been obtained, it appears that a single molecule of AlH_2Cl behaved both as a Lewis acid and the hydride ion donor to yield β-oriented glycol ether. Since AlH_2Cl is a weaker Lewis acid than either $AlCl_3$ or $AlHCl_2$ it can be assumed that the reaction proceeds through a transition state of the type shown in the scheme - 1.

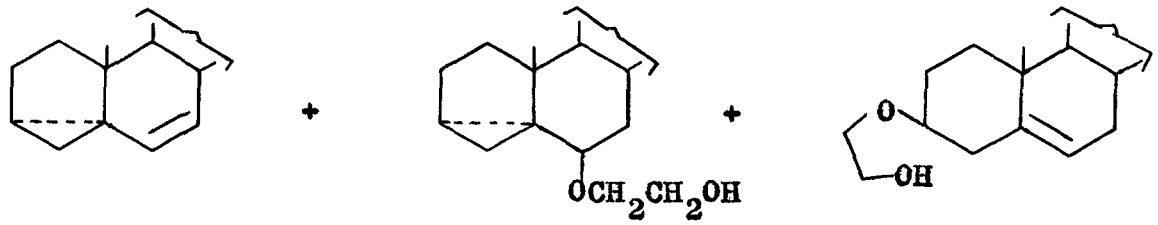
Scheme - 1



It is interesting to note that 6,6-ethylenedioxy-3α,5-cyclo-5α-cholestane (XXIV) as compared to other acetals showed different behaviour towards $LiAlH_4$-$AlCl_3$(1:1). In view of the above mentioned mechanism of hydrogenolysis of steroidal cyclic acetals, the formation of the hydrocarbon (XXVI) and isomeric hydroxyether (XXIX) directly from the acetal (XXIV) is not possible. According to the accepted mechanism of hydrogenolysis of steroidal cyclic acetals by $LiAlH_4$-$AlCl_3$ (1:1) the reducing species attacks the rear oxygen of the acetal moiety leading to the species (XXIVa).



(XXIV) (XXV) (XXVI)



(XXVII) (XXVIII) (XXIX)

The latter undergoes a hydride shift to give (XXIVb) which on subsequent hydrolysis provides the hydroxy ether (XXVIII). The species (XXIVb) may react further with another molecule of AlH_2Cl to give the homoallylic cation (XXXII) via the intermediate (XXIVc). The intermediate cation (XXXII) may lead to all the observed products.

I.R. and n.m.r. values of some steroidal acetals and their products of mixed hydride ($LiAlH_4$-$AlCl_3$, 1:1) reduction are assembled in Table II.

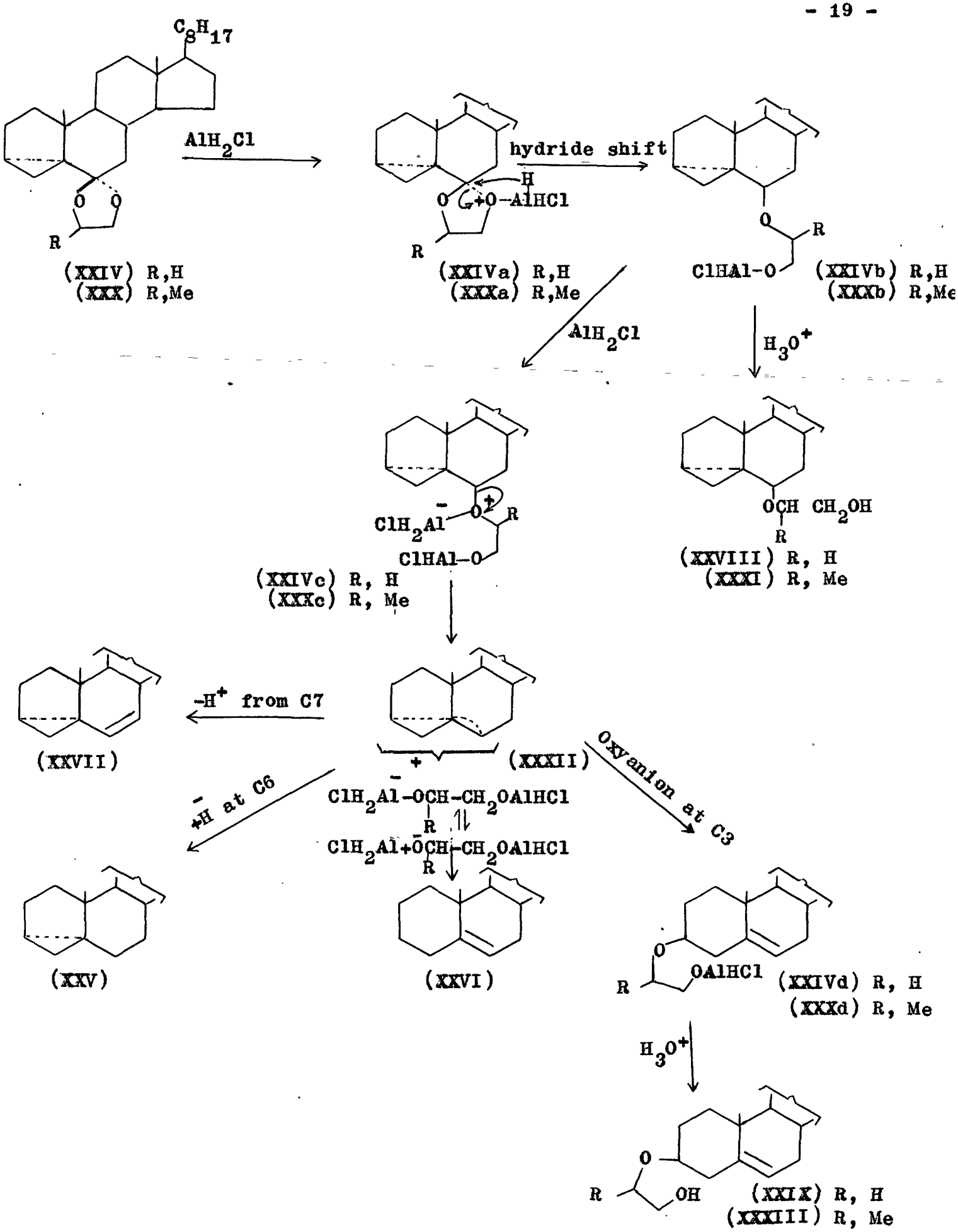

C_8H_{17}
AlH_2Cl
hydride shift
(XXIV) R,H
(XXX) R,Me
(XXIVa) R,H
(XXXa) R,Me
ClHAl-O
(XXIVb) R,H
(XXXb) R,Me
AlH_2Cl
H_3O^+
ClH_2Al
ClHAl-O
(XXIVc) R, H
(XXXc) R, Me
OCH CH_2OH
(XXVIII) R, H
(XXXI) R, Me
$-H^+$ from C7
(XXVII)
(XXXII)
Oxyanion at C3
$-H^+$ at C6
ClH_2Al-OCH-CH_2OAlHCl
R
ClH_2Al+OCH-CH_2OAlHCl
R
(XXV)
(XXVI)
OAlHCl
(XXIVd) R, H
(XXXd) R, Me
H_3O^+
OH
(XXIX) R, H
(XXXIII) R, Me

TABLE - II

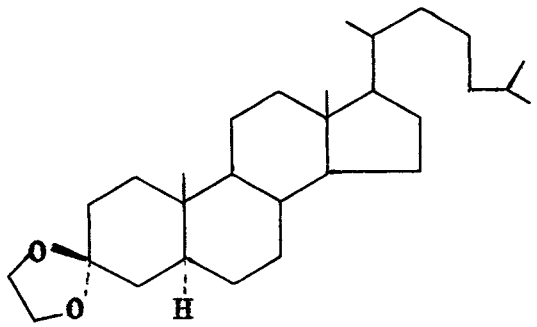
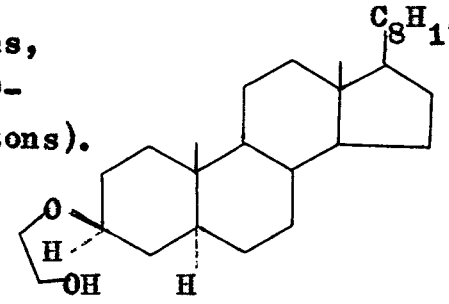
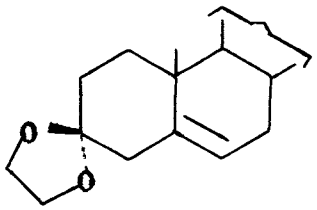
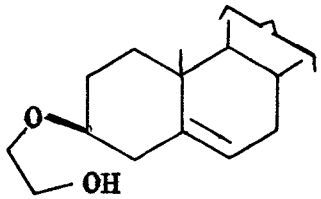
Starting material	I.r. and n.m.r.	Product/s	I.r. and n.m.r.	Ref.
 3,3-ethylenedioxy-5α-cholestane	$\nu_{max.}$ 1133m, 1111m, 1093m, 1081m, 1047s, 1026s cm^{-1} (C-O-); δ 3.92 (4 protons, O-CH_2-CH_2-O-), 0.92 (C19-protons), 0.63 (C18-protons).	 3β-(2'-hydroxyethoxy)-5α-cholestane	$\nu_{max.}$ 3410(OH), 1110, 1058 cm^{-1}(C-O-); δ3.23(3α-H, $W_{\frac{1}{2}}$ 12 cps, axial); 3.65 u.m.c. (C_3-O-CH_2-CH_2-OH); 0.6, 0.8, 0.9 (five methyl groups).	61
 3,3-ethylenedioxy cholest-5-ene	$\nu_{max.}$ 1626 (C=C), 1120s, 1040s, 1026s cm^{-1}(C-O-); δ3.99s (4 protons, O-CH_2-CH_2-O-), 5.3 u.m.c. (C_6-vinylic proton), 1.01 (C_{19}-protons), 0.66 (C_{18}-protons), 0.8, 0.9, 0.96 (other methyl groups).	 3β-(2'-hydroxy-ethoxy)cholest-5-ene	$\nu_{max.}$ 3405(OH), 1630w (C=C), 1110s, 1060s cm^{-1}(C-O-); δ3.22 (3α-H, $W_{\frac{1}{2}}$ 12 cps, axial); 3.68 u.m.c. (-O-CH_2-CH_2-OH), 5.35br u.m.c. (C_6-vinylic proton), 0.6 (C_{18}-protons), 1.01 (C_{19}-protons), 0.8, 0.9, 0.96 (other methyl groups).	61

TABLE - II (Contd.)

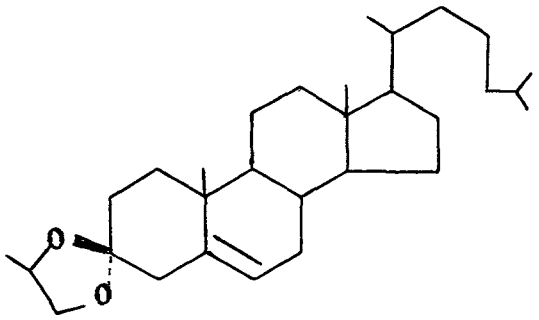
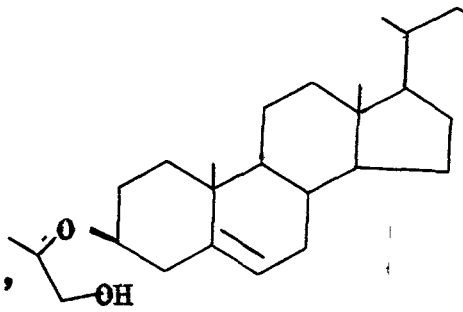
Starting material	I.r. and n.m.r.	Product/s	I.r. and n.m.r	Ref.
 1'-methyl-3,3-ethylenedioxycholest-5-ene	$\nu_{max.}$ 1626 (C=C), 1120s, 1040s, 1026s cm^{-1} (C-O-); δ 3.3d (J=6 cps) ($-O-\underline{CH}_2-\underset{CH_3}{\underset{\vert}{CH}}-O-$), 3.8 umc ($-O-CH_2-\underset{CH_3}{\underset{\vert}{\underline{C}H}}-O-$), 5.16 umc ($C_6$-vinyl proton), 0.66 ($C_{18}$-protons), 0.98 ($C_{19}$-protons); 0.81, 0.9 (other methyl groups), 1.16d (J = 6 cps)(methyl group of Acetal ring).	 3β-(1'-methyl-2'-hydroxyethoxy) cholest-5-ene	$\nu_{max.}$ 3450(OH), 1640w (C=C), 1075s, 1043 cm^{-1} (C-O-); δ 3.3 umc($-O-\underset{CH_3}{\underset{\vert}{\underline{C}H}}-CH_2OH$), 3.50d (J = 4 cps, $-O-\underset{CH_3}{\underset{\vert}{CH}}-\underline{CH}_2-OH$), 3.71br (3α-$\underline{H}$, $W_{\frac{1}{2}}$ 14 cps, axial) 5.35 mc(C_6-vinyl proton), 1.11d(1'-$\underline{CH}_3$) 1.01 (C_{19}-protons), 0.68 (C_{18}-protons), 0.95, 0.89 and 0.83 (other methyl groups).	61

TABLE - II (Contd.)

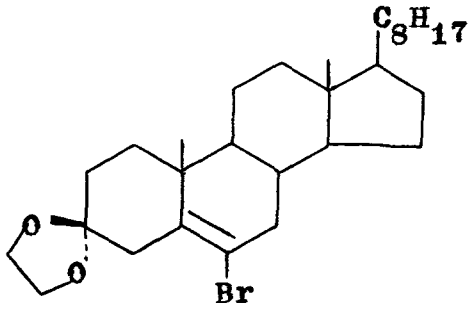
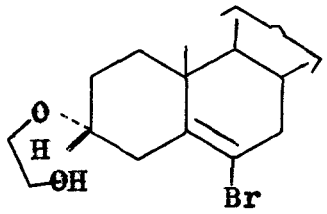
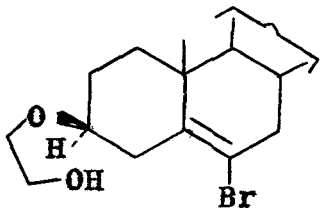
Starting material	I.r. and n.m.r.	Product/s	I.r. and n.m.r	Ref.
 6-bromo-3,3-ethylene-dioxycholest-5-ene.	$\nu_{max.}$ 1662w (C=C), 1210, 1170, 1150, 1095, 1062(C-O-), and 750 cm^{-1} (C-Br); δ 3.94 mc (4 protons, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 1.07, 0.93, 0.90, 0.83, and 0.67 (five methyl groups).	 6-bromo-3α-(2'-hydroxyethoxy) cholest-5-ene.	$\nu_{max.}$ 3430s (OH), 1650w (C=C), 1100, and 1050 cm^{-1}(C-O-); δ3.48 mc (4 protons, -OC$\underline{H}_2$C$\underline{H}_2$OH), 3.27 mc (1 proton, $W\frac{1}{2}$ 5 Hz, C_3^{β}-$\underline{H}$, equatorial), 3.12 (2 protons, C_4-protons), 1.03, 0.92, 0.88, 0.82 and 0.66 (five methyl groups).	60
		 6-bromo-3β-(2'-hydroxyethoxy) cholest-5-ene.	$\nu_{max.}$ 3475br (OH), 1658 (C=C), 1170, 1121, 1068 (C-O-), and 750 cm^{-1} (C-Br); δ 3.64 umc (4 protons, C_3-OC$\underline{H}_2$C$\underline{H}_2$OH), 3.22 br (3 protons, C_3 and C_4 protons), 1.08, 0.96, 0.93, 0.86 and 0.7 (five methyl groups).	

TABLE - II (Contd.)

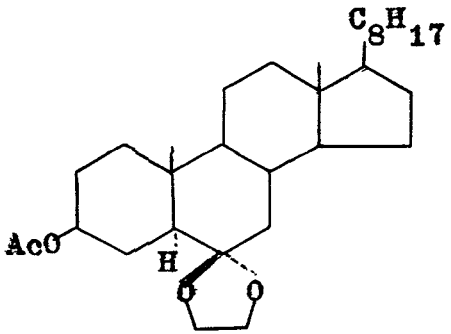
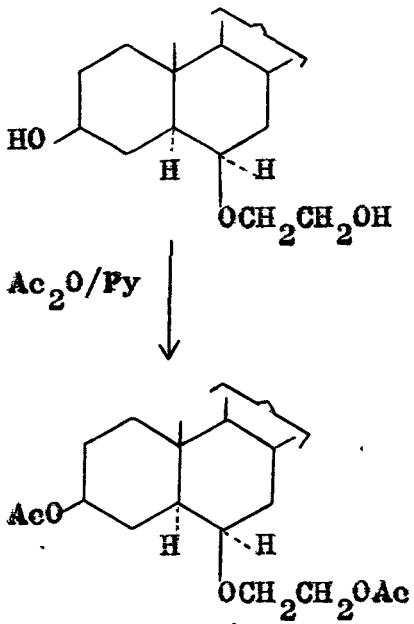
Starting material	I.r. and n.m.r.	Product/s	I.r. and n.m.r.	Ref.
 3β-Acetoxy-6,6-ethylenedioxy-5α-cholestane.	$\nu_{max.}$ 1733s, 1238s (acetate), 1133m, 1111m, 1093m, 1081m, 1047s, 1026 cm^{-1} (C-O-); δ 4.7 br (AcO-C_3^{α}-H), 2.05s (CH_3-COO), 3.8m (4 protons, -OCH_2CH_2O-), 1.01 (C_{10}-CH_3), 0.68 (C_{13}-CH_3).	 3β-Acetoxy-6β-(2'-acetoxyethoxy)-5α-cholestane.	$\nu_{max.}$ 1738, 1240 (ester carbonyl), 1117, 1050, 1026 cm^{-1} (C-O-); δ 4.7 br(C_3^{α}-H, axial), 3.3m (AcOCH_2CH_2O-C_6-H), 3.58 distorted triplet (-O-CH_2-CH_2-OAc); 4.12 distorted triplet (-O-CH_2-CH_2-OAc), 2.05s (6 protons, 2x CH_3COO-).	62

TABLE - II (Contd.)

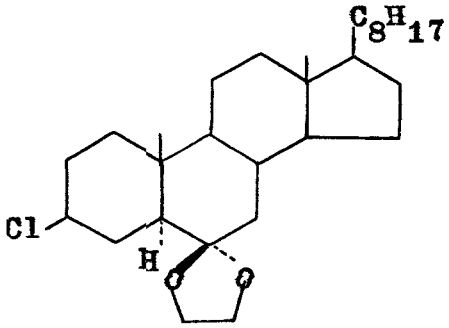
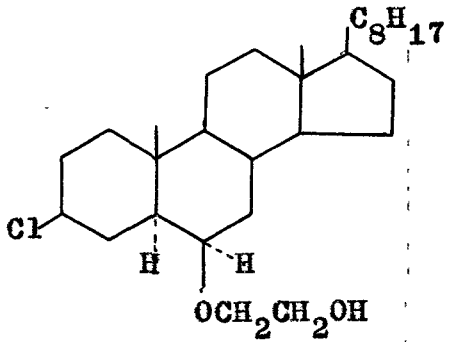
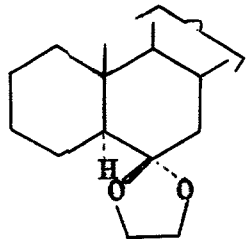
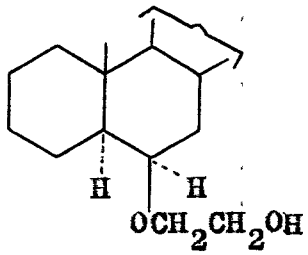
Starting material	I.r. and n.m.r.	Product/s	I.r. and n.m.r.	Ref.
 3β-Chloro-6,6-ethylenedioxy-5α-cholestane.	$\nu_{max.}$ 1176s, 1136s, 1064s, 1042s (C-O-), 763s cm^{-1} (C-Cl); δ3.75 mc (1 proton, C_3^{α}-H), 3.91 mc (4 protons, -O-CH_2-CH_2-O-), 0.67 (C_{18}-protons), 0.97 (C_{19}-protons), 0.94, 0.89 and 0.83 (other methyl groups).	 3β-Chloro-6β-(2'-hydroxyethoxy)-5α-cholestane.	$\nu_{max.}$ 3333br (OH), 1098s, 1052s (C-O-), and 763s cm^{-1} (C-Cl); δ3.70 mc (4 protons, -O-CH_2-CH_2-OH), 3.45 mc (2 protons, C_3^{α}-H and C_6^{α}-H), 1.96 (1 proton, -O-H, exchangeable with deuterium), 0.97 (C_{19}-protons), 0.67 (C_{18}-protons), 0.92 and 0.83 (other methyl groups).	63
 6,6-ethylenedioxy-5α-cholestane.	$\nu_{max.}$ 1133m, 1111m, 1093m, 1081m, 1047s, 1026s cm^{-1} (C-O-); δ0.98(C_{19}-protons), 0.67 (C_{18}-protons), 3.77mc (4 protons, C_6-OCH_2-CH_2-O-).	 6β-(2'-hydroxyethoxy)-5α-cholestane.	$\nu_{max.}$ 3400(OH), 1100, 1048 cm^{-1} (C-O-); δ3.25 (H-C_6-O-, $W\frac{1}{2}$ 5 cps, equatorial), 3.60 umc (C_6-O-CH_2-CH_2-OH), 0.7 (C_{18}-protons), 0.92 (C_{19}-protons), 0.82, 0.89 (other methyl groups).	64

TABLE - II (Contd.)

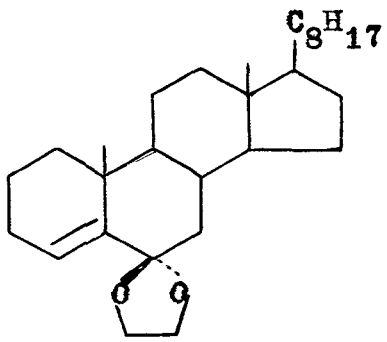
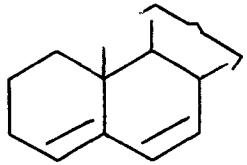
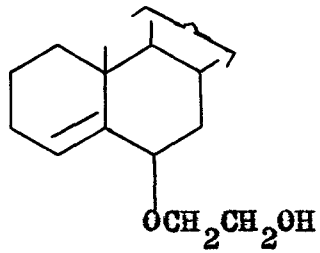
Starting material	I.r. and n.m.r.	Product/s	I.r. and n.m.r.	Ref.
 6→6-ethylenedioxy cholest-4-ene.	$\nu_{max.}$ 1189, 1145, 1137, 1111 and 1085 cm^{-1} (C-O-); δ 5.8t (1-proton, C_4-H), 3.77 mc (4 protons, -O-C<u>H</u>$_2$C<u>H</u>$_2$-O-), 0.92, 0.90, 0.80, 0.70 and 0.67 (five methyl groups).	 Cholesta-4,6-diene +  6β-(2'-hydroxy-ethoxy)cholest-4-ene.	$\nu_{max.}$ 3245br(OH), 1152, 1130, 1120, and 1085 cm^{-1} (C-O-); δ 5.59(1-proton, C_4-<u>H</u>), 3.54 umc (5-protons, C_6-OC<u>H</u>$_2$C<u>H</u>$_2$OH + C_6^{α}-<u>H</u>), 0.96, 0.91, 0.38, 0.80 and 0.64 (five methyl groups).	65

TABLE - II (Contd.)

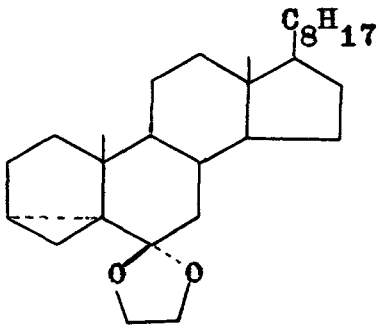
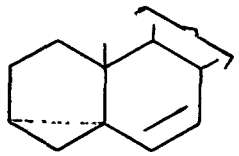
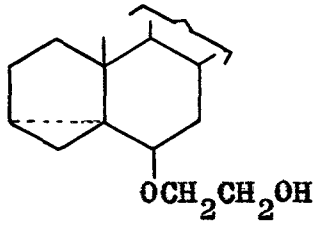
Starting material	I.r. and n.m.r.	Produet/s	I.r. and n.m.r.	Ref.
 6,6-ethylenedioxy-3α,5-cyclo-5α-cholestane.	$\nu_{max.}$ 3040w(Cyclopropane ring), 1040 and 1026 cm^{-1} (C-O-); δ 3.85 mc (4-protons, $-O-C\underline{H}_2-C\underline{H}_2-O-$), a complex between 0.61-0.10 (cyclopropane protons), 0.96 (C_{19}-protons), 0.73 (C_{18}-protons), 0.92 and 0.83 (other methyl groups).	 3α,5-cyclo-5α-cholest-6-ene	$\nu_{max.}$ 3030w, 1010m (Cyclopropane ring), 3010w, 1640w, and 1617w cm^{-1} (C=C); δ 5.33 umc, 5.55 umc (C_6 and C_7 olefinic protons), 0.93, 0.85, and 0.71 (five methyl groups).	63
		+		
		 6β-(2'-hydroxy-ethoxy)-3α,5-cyclo-5α-cholestane.	$\nu_{max.}$ 3333(OH), 1110, and 1056 cm^{-1}(C-O-); δ 3.63 pseudo t (1-proton, $W\frac{1}{2}$ 4 Hz, $C_6^{\alpha}-\underline{H}$, equatorial), 3.55 mc (4-protons, $C_6-O-C\underline{H}_2C\underline{H}_2OH$), a complex between 0.55-0.10 (cyclopropane protons), 0.93, 0.83, and 0.7 (five methyl groups).	

TABLE - II (Contd.)

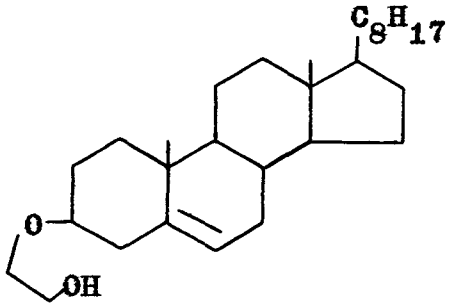
Starting material	I.r. and n.m.r.	Product/s	I.r. and n.m.r.	Ref.
		 3β-(2'-hydroxyethoxy)-cholest-5-ene.	$\nu_{max.}$ 3450(OH), 1630w (C=C), 1110 and 1060s cm^{-1} (C-O-); δ 3.22 (1-proton, $W\frac{1}{2}$ 12 Hz, C_3^{α}-H, axial), 3.68 umc (4-protons, O-CH_2CH_2OH), 5.53 mc (1-proton, C_6-vinyl proton), 0.6 (C_{18}-protons), 1.01 (C_{19}- protons).	

TABLE - II (Contd.)

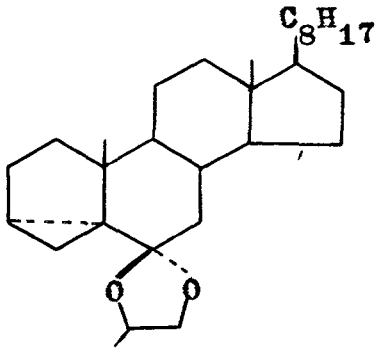
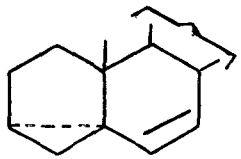
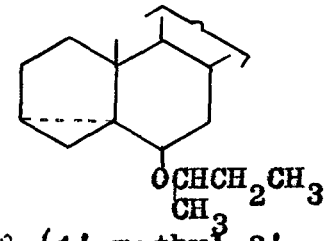
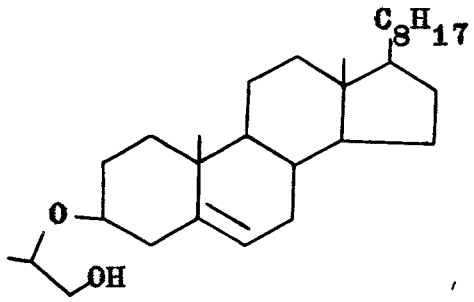
Starting material	I.r. and n.m.r.	Product/s	I.r. and n.m.r.	Ref.
 6,6-(1'-methyl-ethylenedioxy)-3α,5-cyclo-5α-cholestane.	$\nu_{max.}$ 3070, 3030w (cyclopropane ring), 1150m, 1108s and 1090s cm^{-1} (C-O-); δ 3.9 mc (2-protons, $(-OCH_c-(CH_3)CH_aH_b-O-)$, 3.42 mc (1-proton, $-OCH_c-(CH_3).CH_aH_b-O-$), 1.17d (3-protons, J=6 Hz, 1'-CH_3), a complex between 0.6-0.3 (cyclopropane protons), 0.99 (C_{19}-protons), 0.72 (C_{18}-protons), 0.93, 0.89, and 0.83 (other methyl groups).	 3α,5-cyclo-5α-cholest-6-ene. +  6β-(1'-methyl-2'-hydroxyethoxy)-3α,5-cyclo-5α-cholestane.	$\nu_{max.}$ 3030w, 1010m(cyclopropane ring), 3010w, 1640w and 1617w cm^{-1} (C=C); δ 5.33 umc, 5.55 umc (C_6 and C_7 olefinic protons), 0.93, 0.85 and 0.71 (five methyl groups). $\nu_{max.}$ 3380br (OH), 3070, 3030w (cyclopropane ring), 1150m, 1108s, and 1090 cm^{-1} (C-O-); δ 3.3 mc (4-protons, $C_6-O-CH(CH_3)CH_2-OH + C_6-H$), 2.1s (1-proton, -O-H, exchangeable with deuterium), 1.07d (3- protons, J=6 Hz, 1'-CH_3), a complex between 0.6-0.3 (cyclopropane protons), 0.90, 0.82 and 0.68 (five methyl groups).	60

TABLE - II (Contd.)

Starting material	I.r. and n.m.r.	Product/s	I.r. and n.m.r.	Ref.
		 3β-(1'-methyl-2'-hydroxyethoxy)cholest-5-ene.	2) $\nu_{max.}$ 3450(OH), 1640w(C=C), 1075s and 1043 cm^{-1}(C-O-); δ3.33 (1-proton, C3-OC<u>H</u>(CH_3)CH_2OH), 3.50d (2-protons, J=4 Hz, OCH(CH_3)C<u>H_2</u>OH), 3.71br (1-proton, $W\frac{1}{2}$ 14 Hz, C_3^{α}-<u>H</u>, axial), 5.35 mc (1-proton, C_6-<u>H</u>), 1.11d (1'-C<u>H_3</u>), 1.01 (C_{19}-protons), 0.68 (C_{18}-protons), 0.95, 0.89 and 0.83 (other methyl groups).	

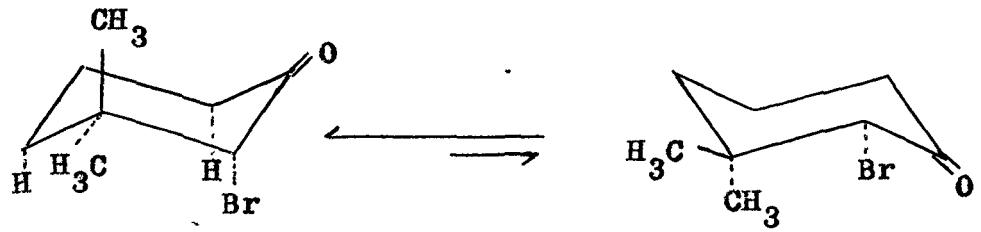
α-Bromination of Ketones:

The α-bromination of ketones as it is ordinarily conducted namely, in the presence of added or generated hydrogen bromide, results in the thermodynamically more stable product. Kinetically controlled bromination may be effected by carrying out the reaction in the presence of an agent capable of removing hydrogen bromide as it is formed, e.g., sodium acetate, or by brominating the corresponding enol acetate in the presence of pyridine, sodium acetate or epichlorohydrin. The kinetic product may be the same[66] as the thermodynamic one or different[67-69] from it depending upon steric factors.

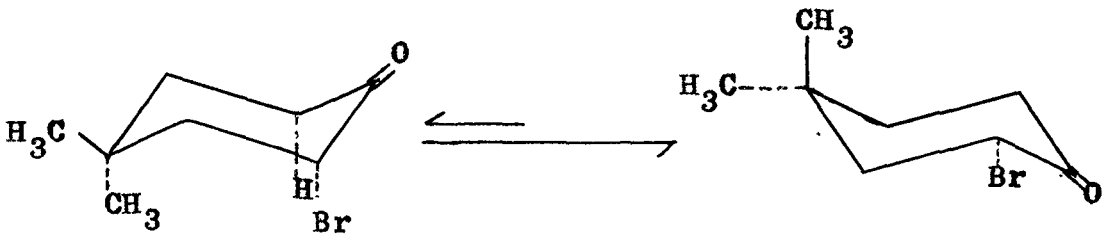
Base - catalysed bromination of methylene and methyl ketones cannot be stopped at the monobromoketone stage. After complete bromination occurs, the polybromoketones are cleaved under the basic reaction conditions.

Since the isolated cyclohexane ring is non-rigid and can flip from one chair form to the another, a 2-bromocyclohexanone is free to assume whichever chair conformation accords maximum stability to the molecule. By infrared spectroscopy, Corey[70] identified the stable forms of a series of methylated 2-bromocyclohexanones and found that the orientation of bromine in the stable conformation is sometimes axial and sometimes equatorial. Thus in the case of 2-bromo-3,3-dimethylcyclohexanone, the stable

conformation is Br-axial (a-XXXIV), and in the 4,4-dimethyl isomer it is Br-equatorial (e-XXXV). Corey[70] considers relative stability to be determined by the operation of two opposing effects. One, the steric effect, is the sum of non-bonded repulsive interactions which tend to destabilize the Br-axial form.



(a-XXXIV) (e-XXXIV)

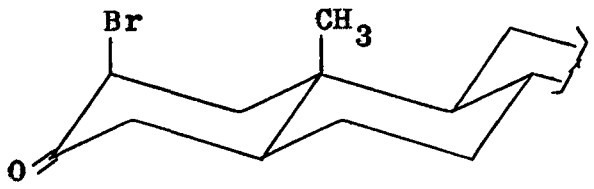


(a-XXXV) (e-XXXV)

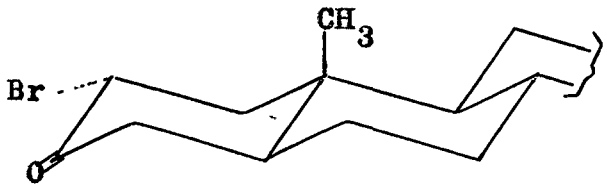
In (a-XXXIV), two 1:3 H:Br interactions produce a weak steric effect. A second electrical effect, which destabilizes a Br-equatorial ketone is due to electrical repulsion between the C-O and C-Br dipoles. Electrical repulsion is estimated to

destabilize (e-XXXIV) to the extent of some 2.7Kcal/mole, while steric interactions destabilize (a-XXXIV) by only about 0.4 Kcal/mole. In the case of 2-bromo-4,4-dimethylcyclohexanone, however, steric repulsion between axial bromine and axial methyl in (a-XXXV) outweighs the electrical effect in (e-XXXV) and the Br-equatorial form is the more stable.

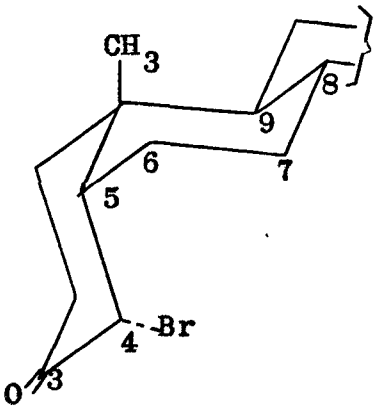
A steroid bromoketone is rigid in the sense that ring flip is not possible, and the conformation of maximum stability is not attained automatically. Indeed a few of the bromoketones in both labile and stable forms, usually recognizable from observation that under catalysis by hydrogen bromide the former can be isomerized to the latter; these compounds are all of the type -CHBrCO-, and equilibration is achieved through the enol form. From estimates of the relative magnitudes of the two effects based on stability relationships in the cyclohexane series, Corey[70] deduced the relative stabilities of the epimeric bromo derivatives of steroids. Thus 2β-bromocholestanone (a-XXXVI) is destabilized by a Br:CH_3 interaction, and 4α-bromocoprostanone (a-XXXVII) is subject to interaction of bromine with carbon atoms 7 and 9, and the products of expected greater stability, 2α-bromocholestanone (e-XXXVI) and 4β-bromocoprostanone (e-XXXVII) are indeed stable and are the only epimers that have been isolated as bromination products.



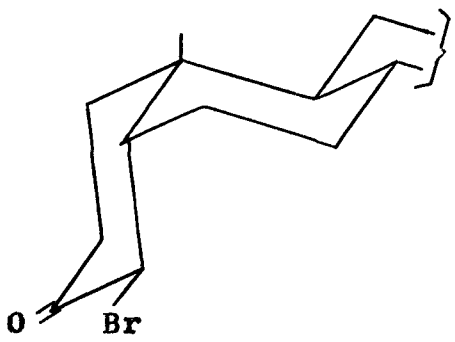
(a-XXXVI)



(e-XXXVI)



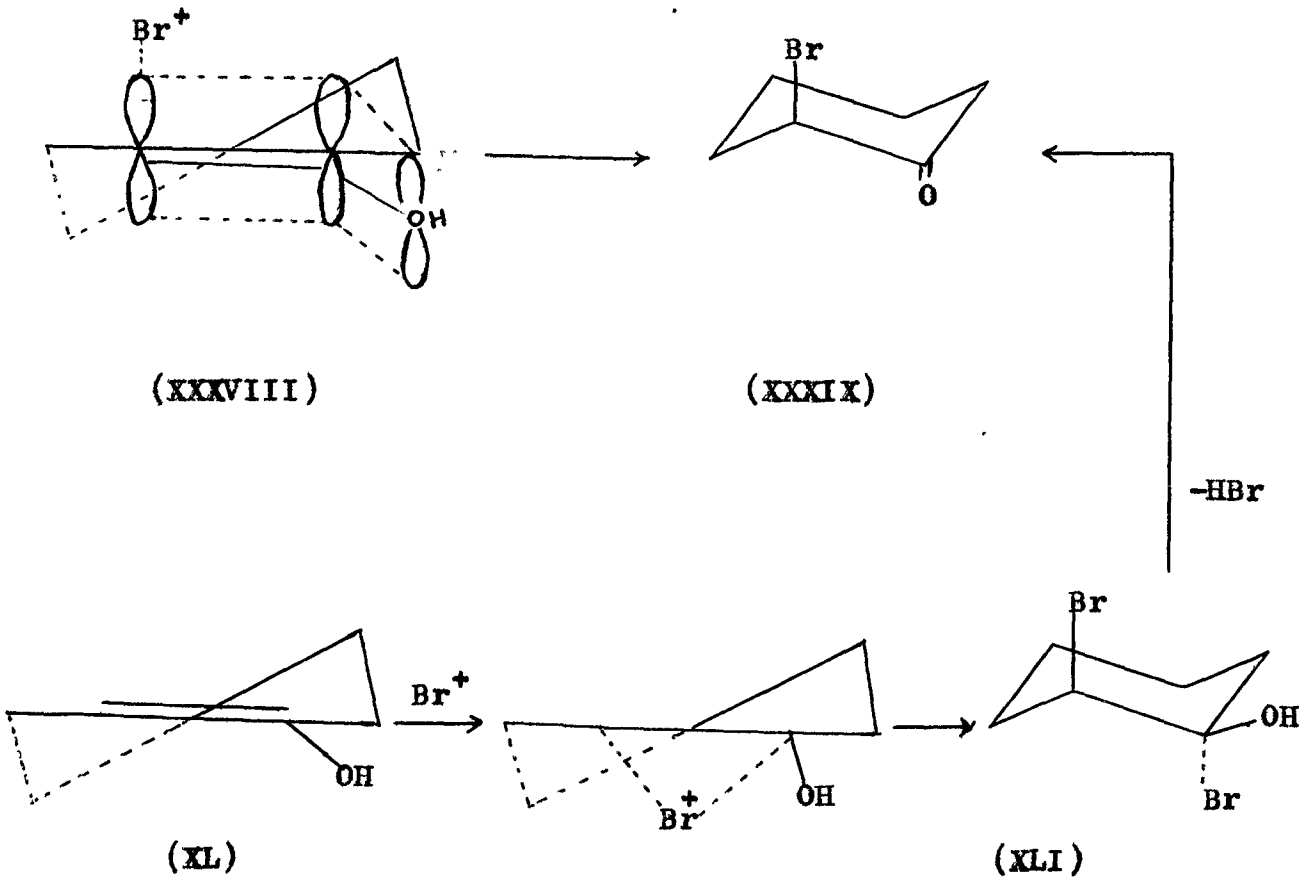
(a-XXXVII)



(e-XXXVII)

Corey[71] noticed that in those instances where both labile and stable epimers have been isolated the initially formed labile compound is Br-axial, an indication that the axial epimer is formed faster than the equatorial one. Thus it is assumed that in the bromination of cholestanone and coprostanone the axial epimers are the initial products but are so labile that they have escaped isolation. Two interpretations that have been advanced for preferential axial bromination are formulated for

the case of cyclohexanone, reacting as the enol of half chair conformation (XL). Corey[71] noted that in the formation of the axial products (XXXIX), but not of the equatorial isomer, the π - orbitals of the enol are arranged favourably for efficient overlap in the transition state (XXXVIII) with an orbital left vacant by the departing α-hydrogen atom. An alternative explanation[72] is that the reaction involves a cyclic bromonium ion (α or β), which by diaxial opening (XLI) and elimination affords the axial α-bromoketone.

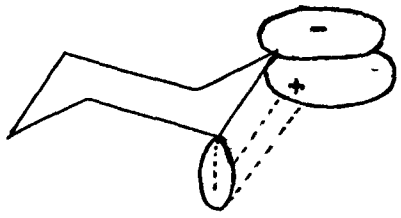


The stereochemistry of enolization of 3β-acetoxycholestan-7-one to the Δ^6-en-7-ol and of the ketonization of this enol have been studied using deuterium tracer with HBr as a catalyst in $CHCl_3$ solution. The axial hydrogen at C6 is lost in enolization 1.2 times as rapidly as the equatorial hydrogen. For the reverse reaction, ketonization, an axial hydrogen is gained 1.5 times as rapidly as an equatorial hydrogen. The values indicate that despite a strong steric retardation of the gain and loss of an axial hydrogen, axial attack is still at least as favourable as equatorial attack. Correction for this steric effect gives the result that 'stereoelectronic factors' favour axial attack over equatorial attack by a factor of atleast 12. The acetic acid catalysed enolization-ketonization reaction is even more specific and axial attack is favoured over equatorial attack by a total factor of at least 9 with a stereoelectronic component of at least 50.

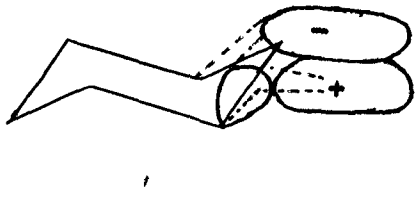
Bromination of steroidal ketones via enoles is characterized in several cases and perhaps generally by an effect which directs the incoming bromine substituent to the axial rather than the equatorial position. Opposing this effect is the classical steric effect which directs a large substituent such as (Br) to the less crowded equatorial orientation. The net result of these two effects which influence the relative rates of formation of the epimers with axial and equatorial

bromine is clear in those cases where the bromoketone which is isolated as the unstable epimer, formed for kinetic rather than for steady state reasons. In such instances the importance of the nonsteric effect is apparent since the major product has invariably been found to be the epimer with axial bromine.

Orienting influence which is responsible for this stereochemical preference is stereochemical-electronic in nature and depends upon the degree of delocalization of electrons in purturbed axial and equatorial bonds which are α to an exocyclic π -orbital. The following figure indicates the relationship between stereochemical orientation and the extent of delocalization of exocyclic δ -electrons to an adjacent exocyclic π -orbital. Since the transition state for enolization-ketonization type processes is stabilized by bonding between the α-carbon and carbonyl carbon atom involving δ -π delocalization as shown in the following figures.



axial interaction
(bonding)



equatorial interaction
(non-bonding)

There should be preference for loss or gain of an axial α-substituent over an equatorial α-substituent or there is better bonding in the transition state for enolization-ketonization when an entering or leaving α-substituent possess the axial orientation than the alternative equatorial orientation. Because the structure of the transition state for such processes is intermediate between the structures of the enol and ketone or ketone conjugate acid, the bond being formed to or broken from α-carbon will not possess pure axial or equatorial character and the considerations expressed in figure above are extreme. However, as the transition state structure approaches that of the ketone, the magnitude of the stereoelectronic discrimination should increase in favour of axial attack.

Corey[71] has represented the methods for predicting the orientation of bromine in all α-bromoketosteroids with ketone function in ring A, B or C and A/B cis or trans. One method applies to α-bromoketosteroids whose stereochemistry is thermodynamically controlled and the other method applies to α-bromoketosteroids whose stereochemistry is kinetically controlled. In every case there is agreement between predicted and determined configuration at C(Br). A number of cases are reported in which prediction has led to a redetermination and eventual reassignment of configuration. In other cases, configurations, which are consistent with predictions, are assigned for the first time

using both infrared and chemical evidence. Thus it has been shown in accord with expectation, that the bromination of 5α, 6β-dibromocholestan-3-one produced the 4α-derivative faster than the 4β-derivative although the latter is the more stable. Likewise the bromination of 3α-acetoxycholestan-6-one afforded, as predicted, the 5α-bromo derivative which is isomerized to the 7α-bromo derivative by hydrogen bromide.

Kinetically Controlled Bromination Products: The rule which has been developed for predicting the stereochemistry of the kinetically controlled bromination products of ketosteroids is as "the epimer which is formed faster in the bromination of a ketosteroids is that in which bromine is axial".

A better understanding of the rule may be had by considering the theoretical basis from which it was derived. Ketonization of an enol and the reverse reaction, enolization of a ketone proceed through the same transition state and hence the same geometrical requirements for minimizing the energy of the transition state hold for both reactions. The energy of the transition state for enolization will be at a minimum when there is maximum opportunity for bond formation between the $Sp^3 \longrightarrow$ p-orbital made available by the leaving hydrogen and the p-orbital of the carbonyl carbon.

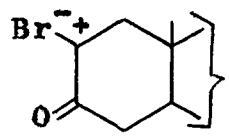
In the case of cyclohexanone this implies that in enolization an axial α-hydrogen is lost in preference to an equatorial α-hydrogen. Furthermore, it follows that in the ketonization of an enolized cyclohexanone (e.g., by bromination or protonation) the incoming substituent should adopt preferentially the axial orientation.

Spectral Studies of α-brominated ketosteroids:

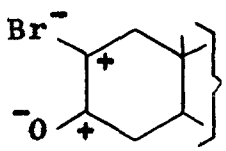
I.R. Spectroscopy - The effect of bromination at the α-carbon atom on the carbonyl stretching bands in the i.r. spectra of ketosteroids is shown to depend on the stereochemical configuration of the C-Br bond[72]. It is suggested that if the bromine atom enters at an equatorial position in cyclohexanone (ring) in the chair conformation, the band is displaced by about 20 cm^{-1} to higher frequency while bromination at an axial position causes very little displacement. These observations aid in the determination of steric configuration and structure of brominated ketosteroids.

There are three factors which might be expected to influence the vibrational frequency of the carbonyl band when a bromine atom is substituted at the α-carbon atom, (i) a mass effect (ii) an electromeric effect transmitted from the C-Br bond through the C-C bond to the C=O bond and (iii) a coulombic field effect produced by the C-Br dipole on the C=O bond.

An increase in the carbonyl frequency could be explained by a mass effect when a light hydrogen atom is replaced by a heavy bromine atom, but it is also discounted by the fact that an ∝-iodine substituent produces a smaller frequency displacement than an ∝-bromine substituent. If the ring A of the steroid nucleus is regarded as cyclohexane ring in the 'chair' conformation, the carbonyl group at position C-3 lies approximately in the plane of the ring and the two C-H bonds at position C-2 are so arranged that while one lies approximately in the plane of the ring (the equatorial bond) the other is perpendicular to this plane (the axial bond). A similar disposition exists at C-4. If a Br atom is introduced at C-2 in the equatorial position the C-Br and C=O bonds will be approximately coplanar and the polarity of the C-Br bond will reduce the polarity of the C=O bond by suppressing the contribution of structure (XLIIb) to the resonance. This would raise the frequency of the carbonyl vibration. If on the other hand, the bromine atom is substituted at an axial position, the C-Br and C=O dipoles lie approximately



(XLIIa)



(XLIIb)

perpendicular to one another and the field effect and accompanying

change of vibrational frequency would be expected to be small.

Carbonyl Band Positions and Postulated Steric Configurations For α-Brominated Ketosteroids.

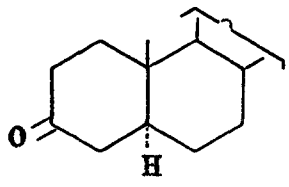
Compound	Carbonyl position (cm^{-1})	Frequency shift on α-bromination	Conformation of C-Br bond	Configuration of C-Br bond	Ref.
Cholestan-3-one	1718	-	-	-	72
2-Iodocholestan-3-one	1724	6	e	α	72
2-Bromocholestan-3-one	1733	15	e	α	72
2,2-Dibromocholestan-3-one	1735	17	e,a	α,β	72
3β-Acetoxycholestan-6-one	1711	-	-	-	71
3β-Acetoxy-5α-bromo-cholestan-6-one	1711	0	a	α	71
3β-Acetoxy-7α-bromo-cholestan-6-one	1713	2	a	α	71

U.V. Spectroscopy - The configuration of the C-Br bond appears also to influence the position and intensity of the U.V. absorption band of the carbonyl chromophores. In 1938, Heilbron and coworkers[73] noticed that the low intensity carbonyl band of the parent ketone (3β-acetoxy-5α-cholestan-7-one) at 287 nm is displaced to 313 nm by the 6β-bromine but is not influenced much by the 6α-bromine atom.

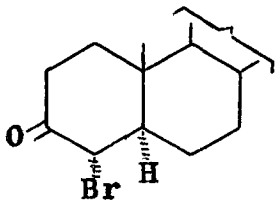
O.R.D. Spectroscopy - Optical rotatory dispersion studies have proved itself a valuable tool in determining the stereochemical, conformational and structural features of several steroidal compounds especially related to the location of a carbonyl function.

O.R.D. of a variety of α-halogenated steroidal ketones has been measured and the resulting curves have been compared with those of the parent ketones. A number of generalizations are made, the most important of which are (a) chlorine and bromine produce essentially the same effect while fluorine behaves in a distinctly different fashion, (b) equatorial chlorine or bromine do not create marked dispersion changes except for minor wavelength shifts generally towards the ultraviolet, (c) axial chlorine or bromine leads to bathochromic shifts which can be correlated closely with the known ultraviolet spectral changes of these chromophores, the amplitude of the dispersion curve is generally increased greatly; the sign of the cotton effect of such axial α-haloketones can be predicted by the emperical 'axial haloketone dispersion rule' thus offering a useful tool for relative and absolute configurational studies.

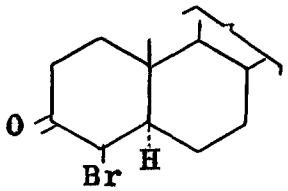
It has been seen in a variety of α-halogenated steroidal ketones that an axial halogen makes substantial change in ORD curve, may sometimes even reverse the sign of the cotton effect e.g.



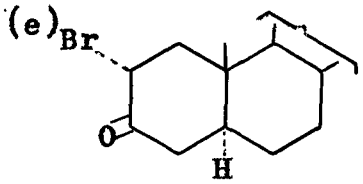
(+ve)



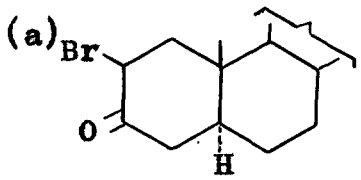
(e)(+ve)
No change



(a)(-ve)



(+ve)
No change

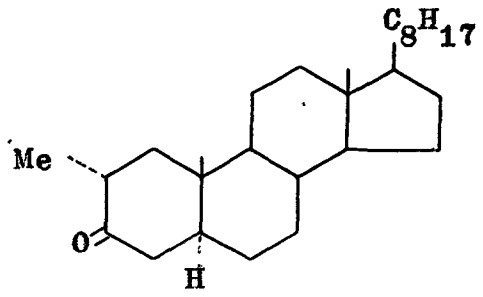


(-ve)
Substantial change

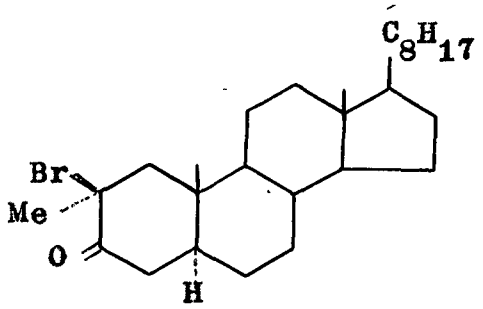
From this observation and many like this, it has been possible to frame α-axial haloketone rule[74] which helps in predicting the sign of the Cotton effect in compounds containing α-axial halogen groups (with respect to carbonyl group) which is very much applicable in locating the position and configuration of halogens in steroidal compounds. The main points of the rule are: (a) An equatorial α-halogen causes no change, and (b) an axial halogen causes change including reversal of the sign of Cotton effect.

This rule is also applicable even in determining the absolute conformation of cyclohexane ring in some steroidal

compounds. For example, 2α-methylcholestane-3-one (XLIIIa) gave one product which on the basis of mechanistic studies and other considerations was formulated as 2β-bromo-2α-methylcholestan-3-one (XLIIIb).

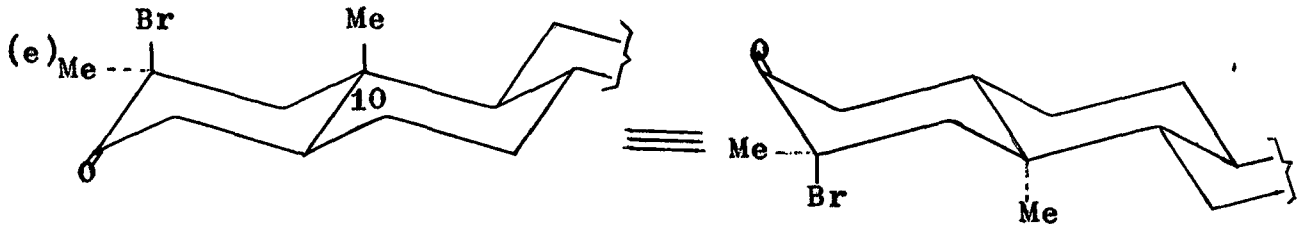


(XLIIIa)



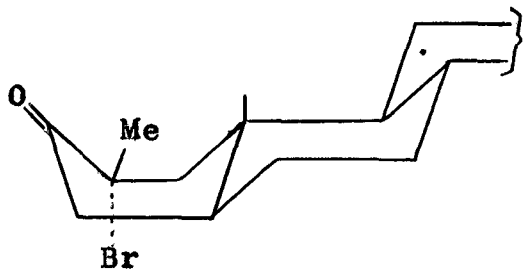
(XLIIIb)

The brominated product showed negative cotton effect while the prediction according to α-haloketone rule is positive.



One suggestion to explain this disparity between prediction and experimentation was to have Br as equatorial and methyl as axial at position 2, which was discarded on the basis of the

rule that α-equatorial halogen makes no substantial change in ORD compared with parent ketone. There is only one convincing way to account for this, that is, if it is assumed that ring A in the compound is in the boat form[75].

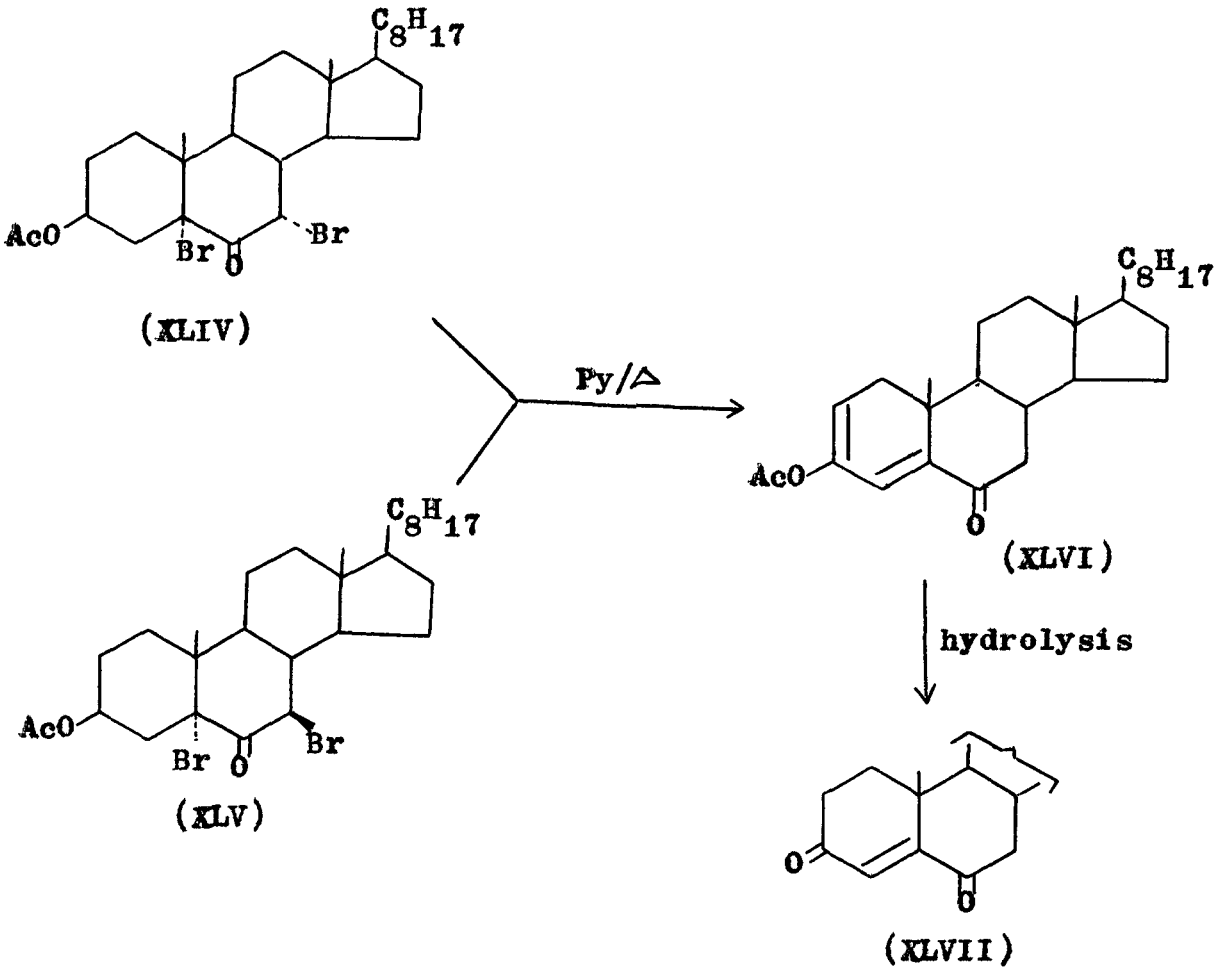


(Predicted-negative)
(Found-negative)

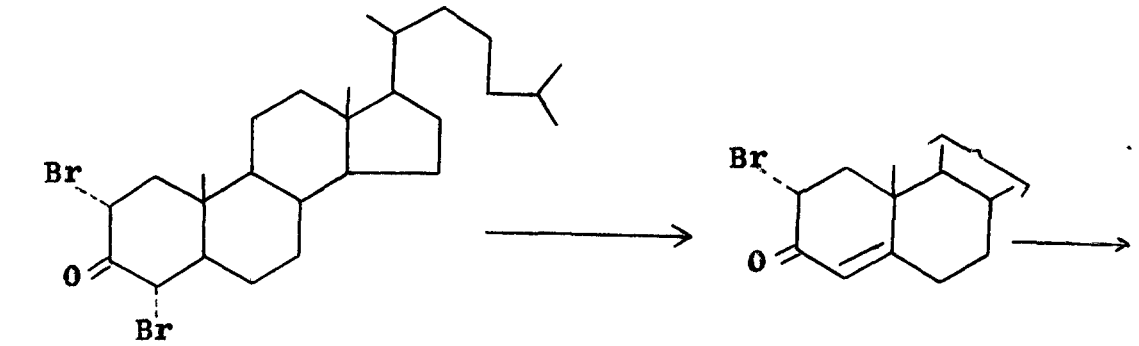
Dehydrobromination of α-Bromoketones

Dehydrobromination of α-bromoketones proceeds well with refluxing bromoketone with pyridine or collidine. Collidine is a useful agent because the insoluble collidine hydrobromide can be used as a quantitative index for the extent of dehydrobromination. However, there are examples where the reaction is accompanied by rearrangement, giving rise to abnormal products.

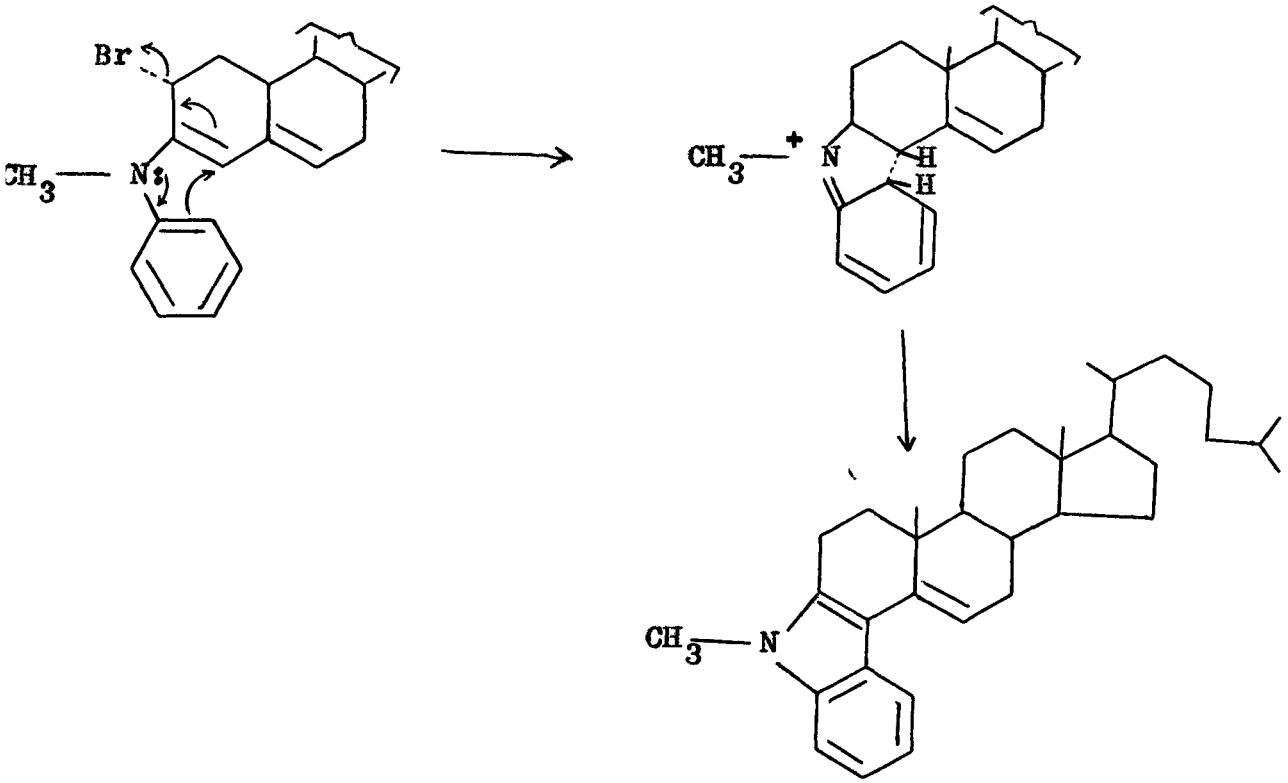
On investigating the dibromination of 6-ketocholestanyl acetate, the Heilbron group[76] isolated two isomers, both shown to be 5,7-dibromides (XLIV) and (XLV) from the observation that on being refluxed with pyridine they yielded as the chief product, the acetoxy dienone (XLVI) converted on hydrolysis into cholest-4-ene-3,6-dione (XLVII).



Warnhoff and NaNongii[77] obtained a product by refluxing 2α,4α-dibromocholestan-3-one (XLVIII) with N,N-dimethyl aniline in an atmosphere of nitrogen which has been shown to be the conjugated indole (L). They suggested the following mechanism for the formation of (L) from (XLVIII).

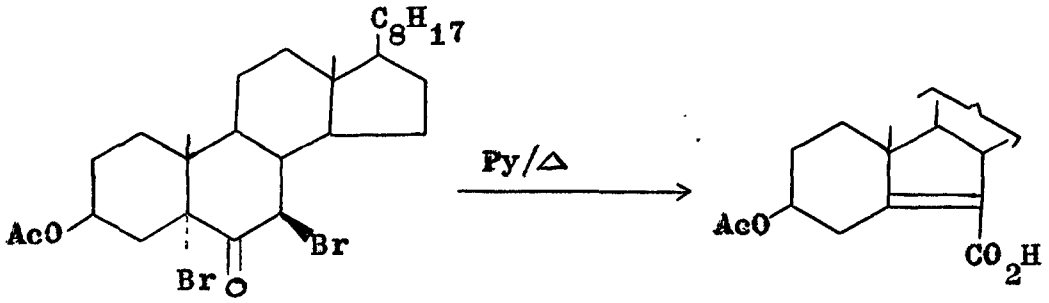


(XLVIII) (XLIX)



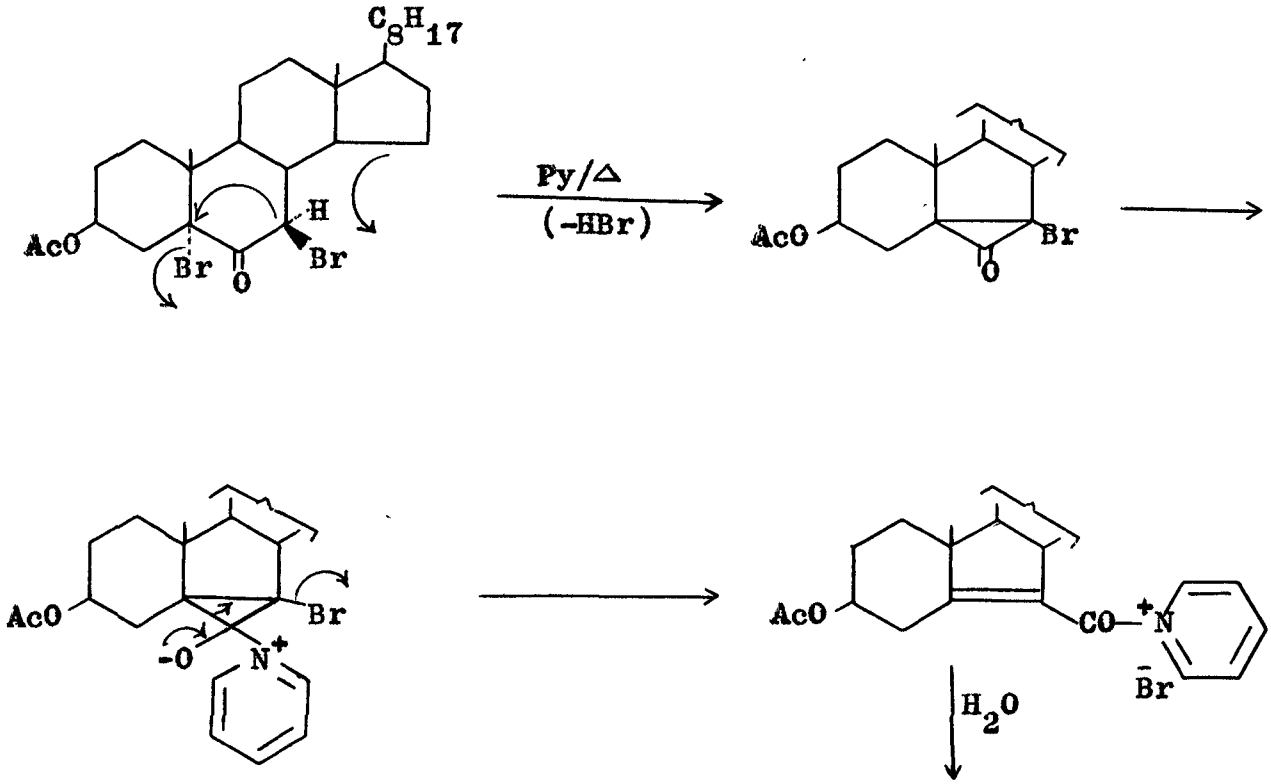
(L)

An interesting example of the Favorskii rearrangement in ring B is afforded by the conversion of 5,7-dibromo-6-ketocholestanyl acetate (XLV) to the ring contracted acid (LI) with hot pyridine[7]



(XLV) (LI)

The mechanism for the formation of (LI) can be suggested as given below.



(LI)

Aromatization of Steroidal Compounds

Aromatization appears to be peculiar to the steroids. Yet if the question is put how can one ring in a polycyclic molecule be selectively aromatized then it becomes a problem in general organic chemistry. If in addition, it is added that this selective aromatization should be accomplished in a molecule where aromatization is, in fact, blocked by the existence of quaternary carbon atoms, then the solution to this problem becomes virtually an unprecedented one in organic chemistry, especially if reasonable yields are desired.

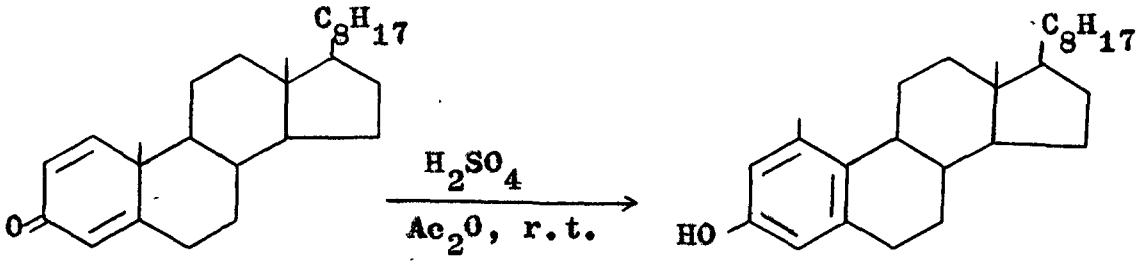
The principal approach to such a problem in organic chemistry has been dehydrogenation. While extremely valuable in structure work, it suffers from a nearly total lack of selectivity, the end product usually being a completely aromatic substance, which is often produced in poor yield. Functional groups, with the exception of lower alkyl substituents, are lost.

In the steroid field, there existed an important incentive to the solution of this problem, namely the partial synthesis of the estrogenic hormones (possessing one aromatic ring) from precursors, which contained four hydroaromatic rings and where simple aromatization was blocked by the presence of two angular methyl groups. In principle, there exist two approaches to the problem-partial aromatization with migration or with elimination of the angular methyl group and both of them were solved.

Subsequently, ring A aromatic steroids became important starting materials in Birch reductions to 19-norsteroids and it was necessary, therefore, to synthesize partially aromatic steroids with a variety of functional groups.

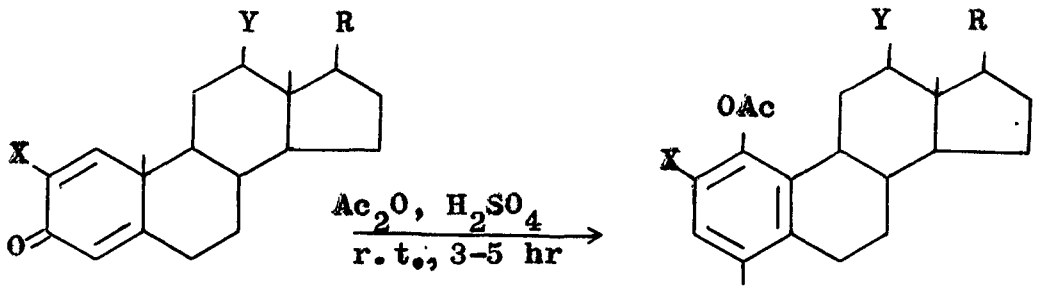
Aromatization of Ring A

Inhoffen and coworkers[79] *reported that the unsaturated* ketone, 1,4-cholestadien-3-one (LII) underwent rearrangement to an isomeric phenol (LIII) with migration of the angular methyl group at C-10, when treated with H_2SO_4 and acetic anhydride at room temperature.



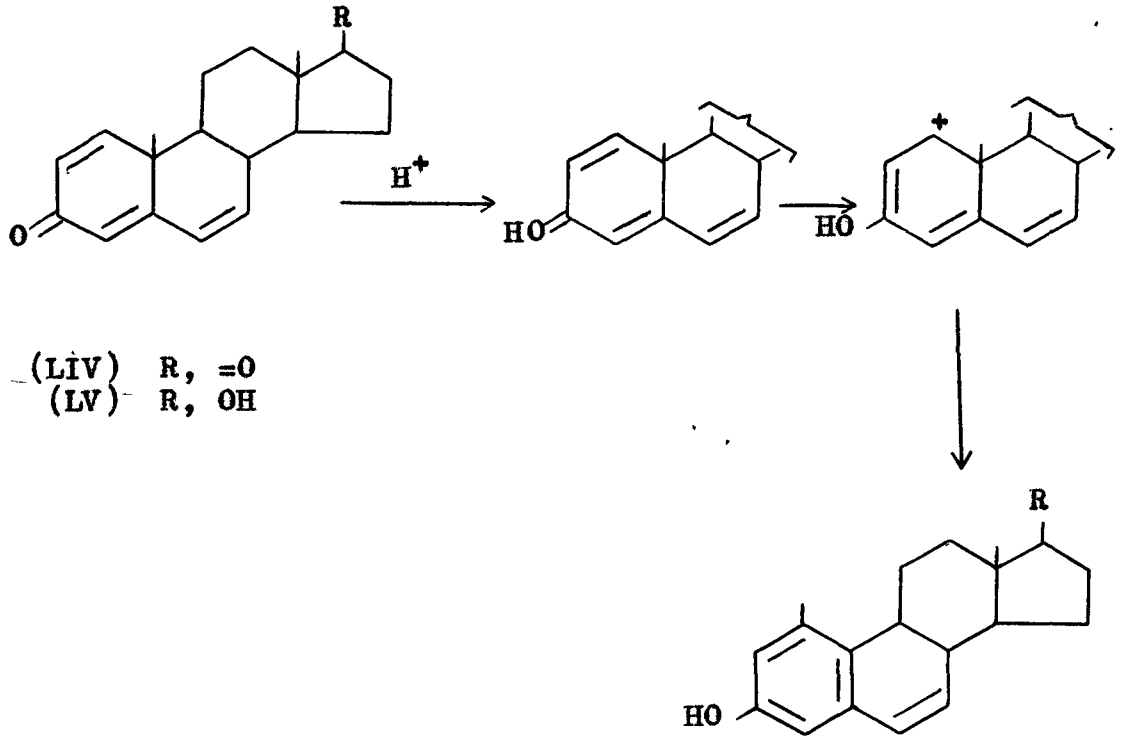
(LII) (LIII)

Further, the substituents may play an important role with respect to the yield of the aromatized compounds as shown below.



R	X	Y	Yield (%)	Ref.
C_8H_{17}	H	H	90	79
OH	H	H	48	80
OH	OMe	H	49	81
OAc	Br	H	53	80
OAc	OAc	H	86	82
=O	H	H	92	79,83,84
C_4H_8COOMe	H	H	85	85
C_4H_8COOMe	H	OAc	45	86
C_4H_8COOMe	H	=O	26	86

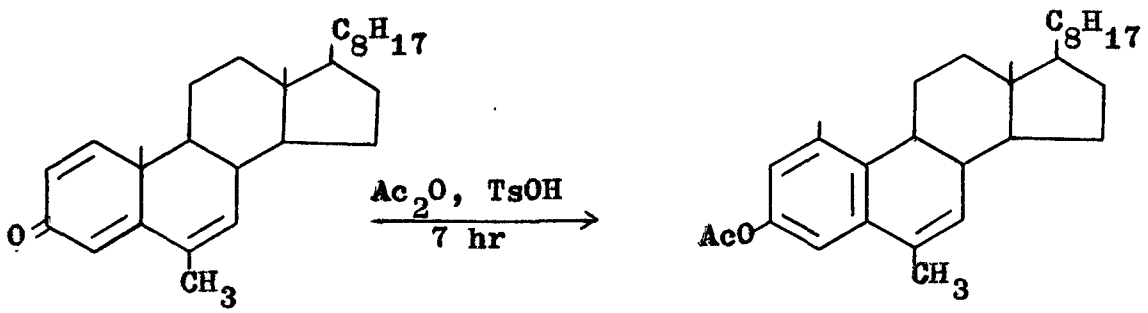
$\Delta^{1,4,6}$-Androstatriene-3,17-dione (LIV) on heating with acetic anhydride-p-toluenesulphonic acid smoothly yielded 1-methyl- Δ^{6}-dehydroestrone (72%)[87] (LVI).



(LIV) R, =O
(LV) R, OH

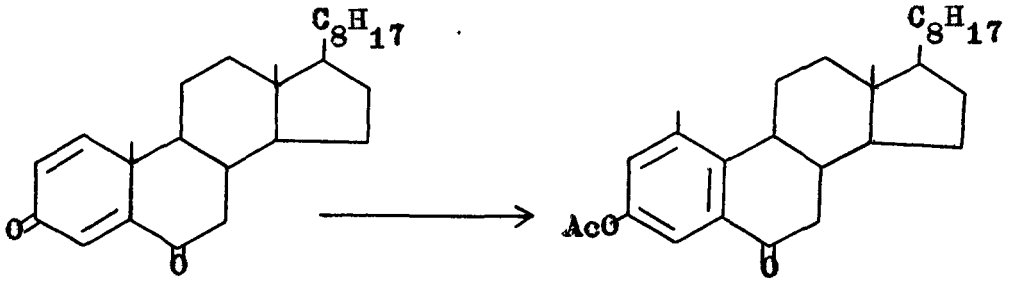
(LVI) R, =O
(LVII) R, OH

6-Methylcholesta-1,4,6-trien-3-one[87] (LVIII) when treated with acetic anhydride and toluene-p-sulphonic acid furnished a product of dienone-phenol rearrangement in satisfactory yield which was characterized as 3-acetoxy-1,6-dimethyl-19-norcholesta-1,3,5(10), 6-tetraene (LIX).



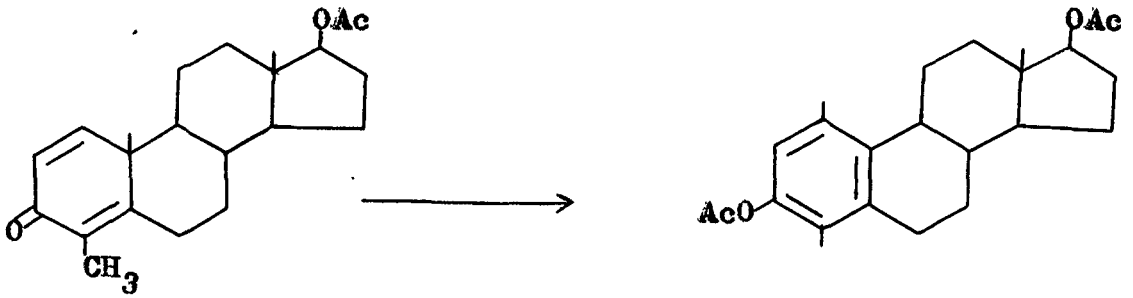
(LVIII) (LIX)

Extension of this process to cholesta-1,4-dien-3,6-dione (LX) furnished 3-acetoxy-1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (LXI)[87].



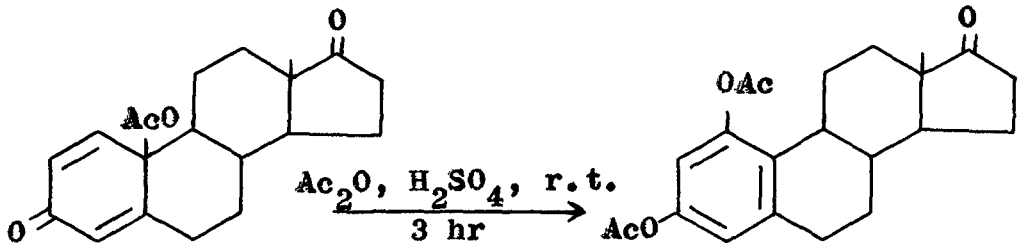
(LX) (LXI)

4-Methyltestosterone acetate (LXII) on treatment with acetic anhydride and toluene-p-sulphonic acid suffered dienone-phenol rearrangement to give 1,4-dimethylestradiol diacetate (LXIII) in 73% yield[88].



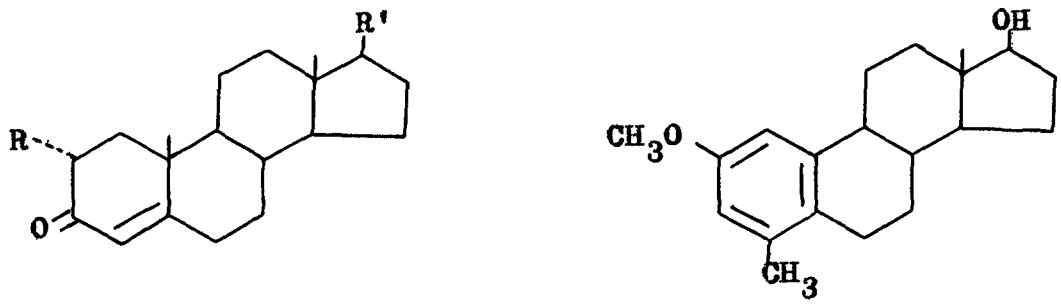
(LXII) (LXIII)

Gold and Schwenk[89] reported that compound containing 10-acetoxyl group (LXIV) underwent rearrangement with the migration of C-10 acetoxyl group to C-1, to give ring A aromatized compound (LXV) when treated with acetic anhydride and sulphuric acid at room temperature.



(LXIV) (LXV)

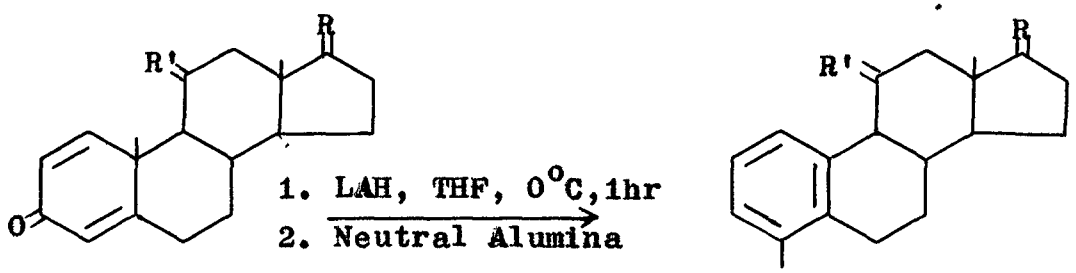
Clarke[80] observed the rearrangement of 2α-hydroxytestosterone (LXVIb) and the . . diacetate (LXVIa) by means of p-toluenesulphonic acid in boiling methanol to 2-methoxy-4-methyl-1,3,5(10)-estratrien-17β-ol (LXVII) in 24 and 11% yields, respectly.



(LXVI) a. R = OAc, R' = Ac
(LXVI) b. R = -OH, R' = OH

(LXVII)

Caspi et al.[90] prepared several deoxysteroids of C-19 series with ring A aromatic by the dienol-benzene rearrangement and the rearrangement is shown to take a uniform course to yield the 4-methyl substituted compounds. For example, 11β-hydroxy androsta-1,4-diene-3,17-dione (LXVIIIa) in anhydrous tetrahydrofuran at 0° was treated with lithium aluminium hydride followed by chromatography over neutral alumina, gave ring A - aromatized compound established as 4-methyloestra-1,3,5(10)-triene-11β,17β-diol (LXIXa).

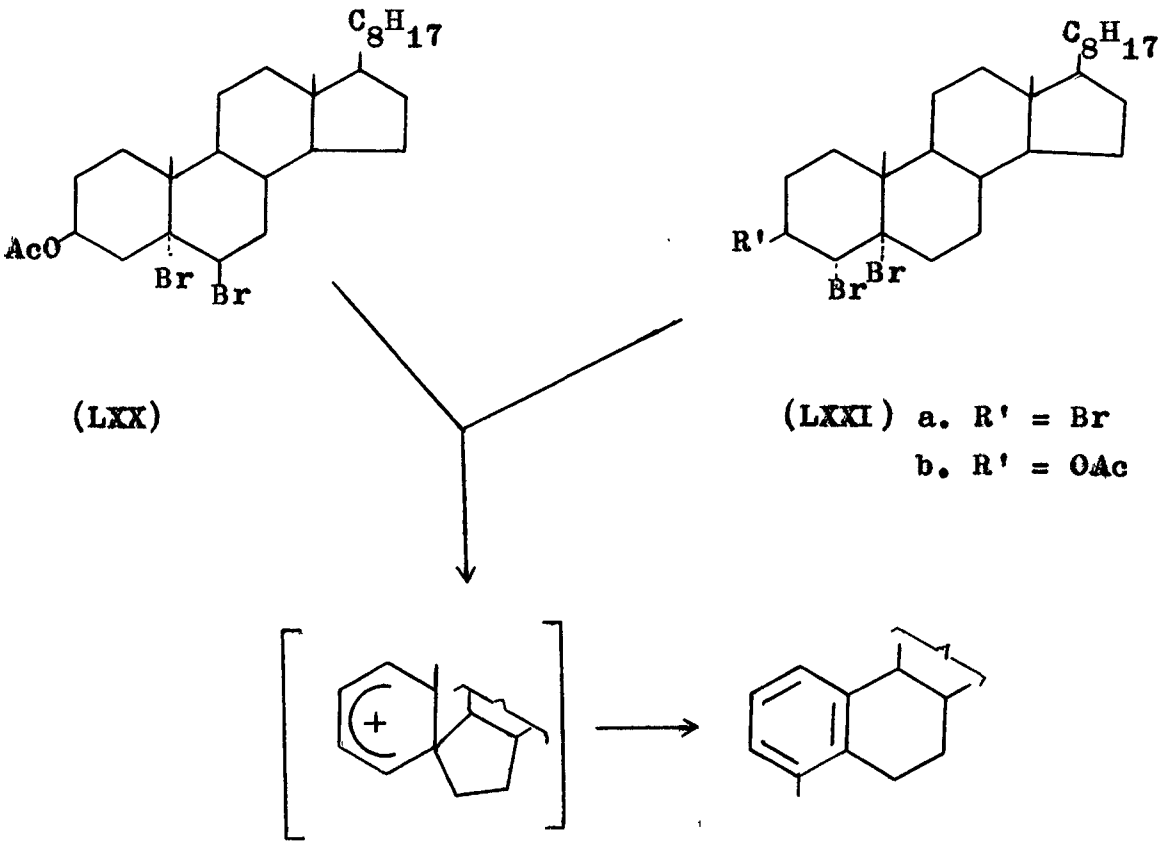


(LXVIII)		(LXIX)	
R	R'	R	R'
a. :O	-OH, ⋯H	a. -OH, ⋯H	-OH, ⋯H
b. :O	:O	b. :O	-OH, ⋯H
c. ⋯OH, $-COCH_2OH$	-OH, ⋯H	c. :O	:O
d. -OAc, ⋯H	H_2	d. -OAc, ⋯H	H_2
e. -OCOEt, ⋯H	H_2	e. -OH, ⋯H	H_2
f. ⋯Me, -OH	H_2	f. :O	H_2

Caspi and Grover[91] discussed the use of different aromatizing catalysts on C-11 oxygenated compounds and found that

anhydrous $AlCl_3$ and neutral alumina gave a mixture of 1-methyl and 4-methyl estratrienes, whereas, BF_3 and aqueous mineral acid gave only the 4-methyl derivatives.

Steroidal compounds (LXX and LXXI) containing three potential sites of unsaturation in rings A and B underwent aromatization into 4-methylestra-1,3,5(10)-triene (LXXII) on treatment with acetyl bromide and hydrogen bromide; under similar conditions mono and bicyclic α,β-unsaturated ketones were also aromatized[92].

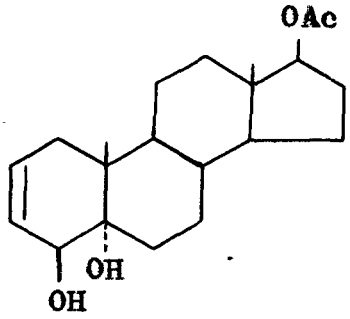


(LXX)

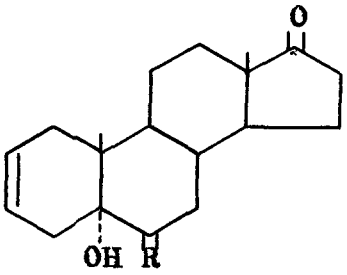
(LXXI) a. R' = Br
b. R' = OAc

(LXXII)

Hanson[93] observed the HBr catalysed aromatization of steroids through spirocationic intermediates produced from substrates containing three potential sites of unsaturation in rings A and B. When the ene diols (LXXIII - LXXV) were heated with HBr in glacial acetic acid under reflux for 10-15 minutes the corresponding 4-methylestra-1,3,5(10)-trienes (LXXVI) and (LXXVII) were formed in 25-30% yield.

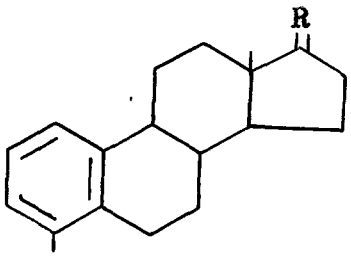


(LXXIII)



(LXXIV) R = H, OH

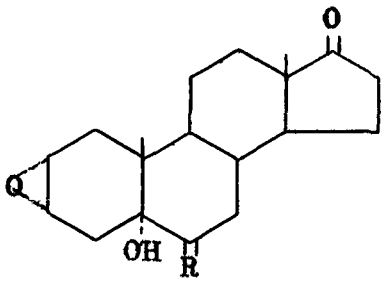
(LXXV) R = OH, H



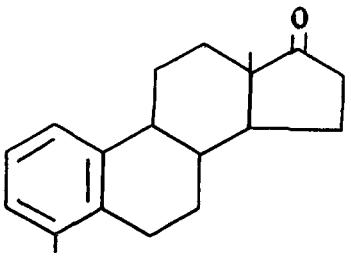
(LXXVI) R = OAc, H

(LXXIII) R = O

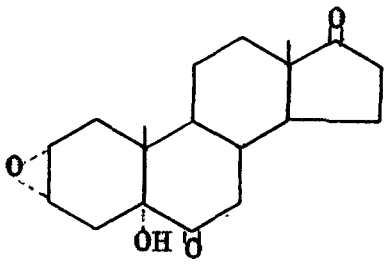
Hanson[94] observed that 2β,3α-epoxy-5α-hydroxyandrostan-17-one (LXXVII) underwent rearrangement to form 4-methylestra-1,3,5(10)-trien-17-one (LXXVIII) on treatment with HBr in glacial acetic acid whilst the corresponding 6-ketone (LXXIX) afforded 1-methylestra-1,3,5(10)-triene (LXXX) on similar treatment.



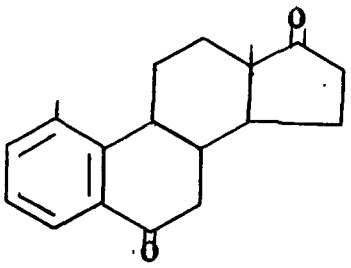
(LXXVII) R = H, H



(LXXVIII)



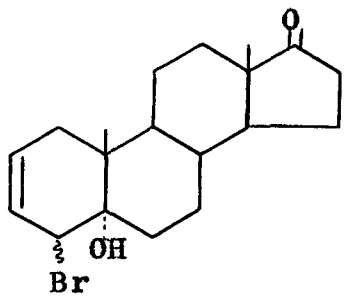
(LXXIX)



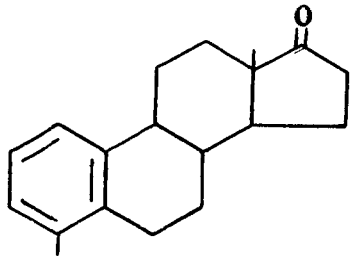
(LXXX)

The presence of a 6-carbonyl group serves, as in the dienone-phenol rearrangement to destabilize a C5 carbonium ion and prevents the formation of spirocyclic intermediates. This leads to aromatization via the alternative pathway of a C-10 → C-1 methyl migration[94].

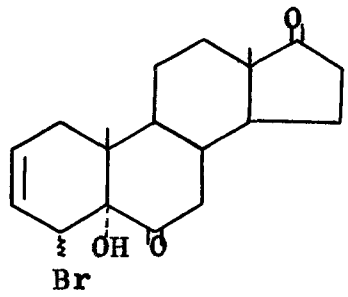
Similar aromatic compounds (LXXVIII) and (LXXX) were also obtained on treatment of Δ^2-4-bromo-5α-hydroxy steroids (LXXXI) and (LXXXII)[94] with HBr in glacial acetic acid.



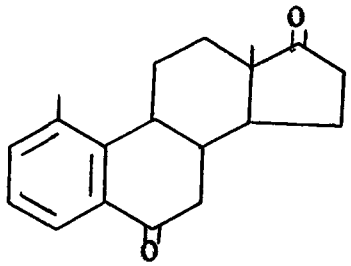
(LXXXI)



(LXXVIII)



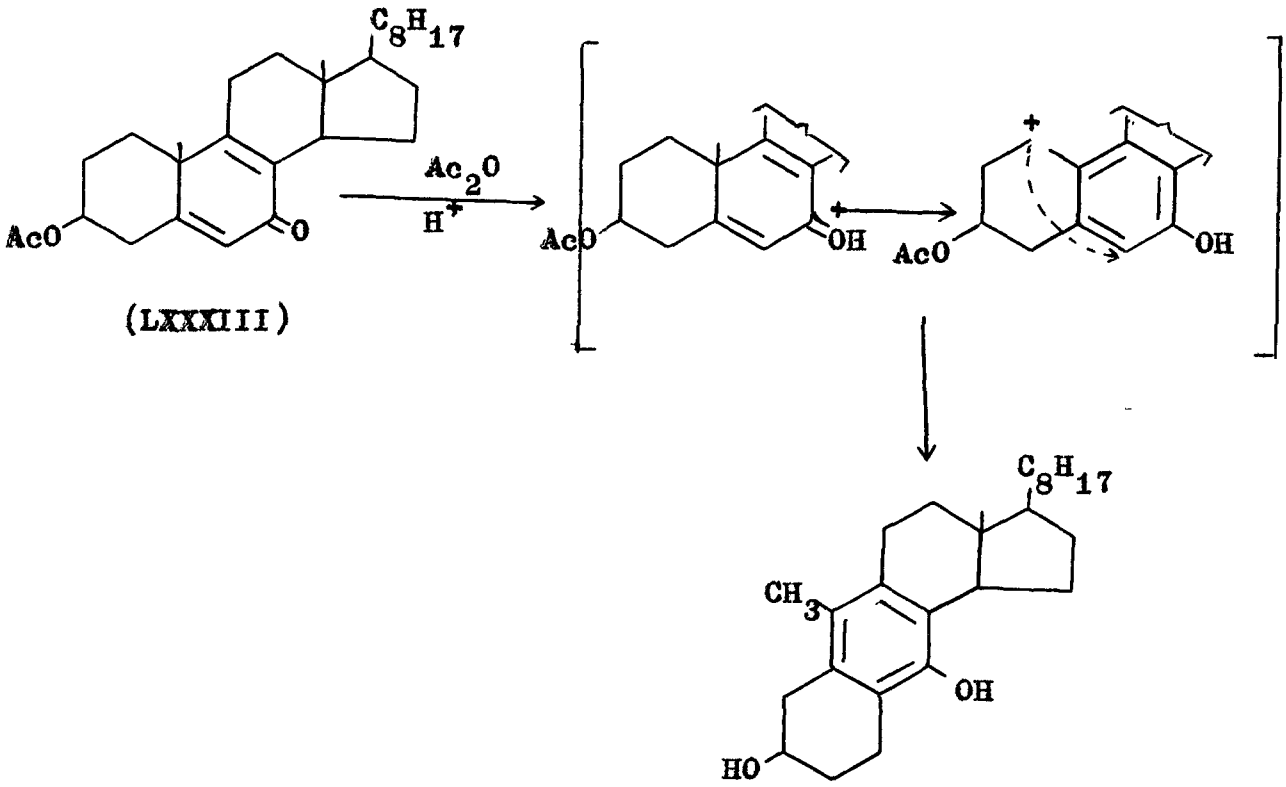
(LXXXII)



(LXXX)

Aromatization of ring B (The Anthrasteroid Rearrangement)

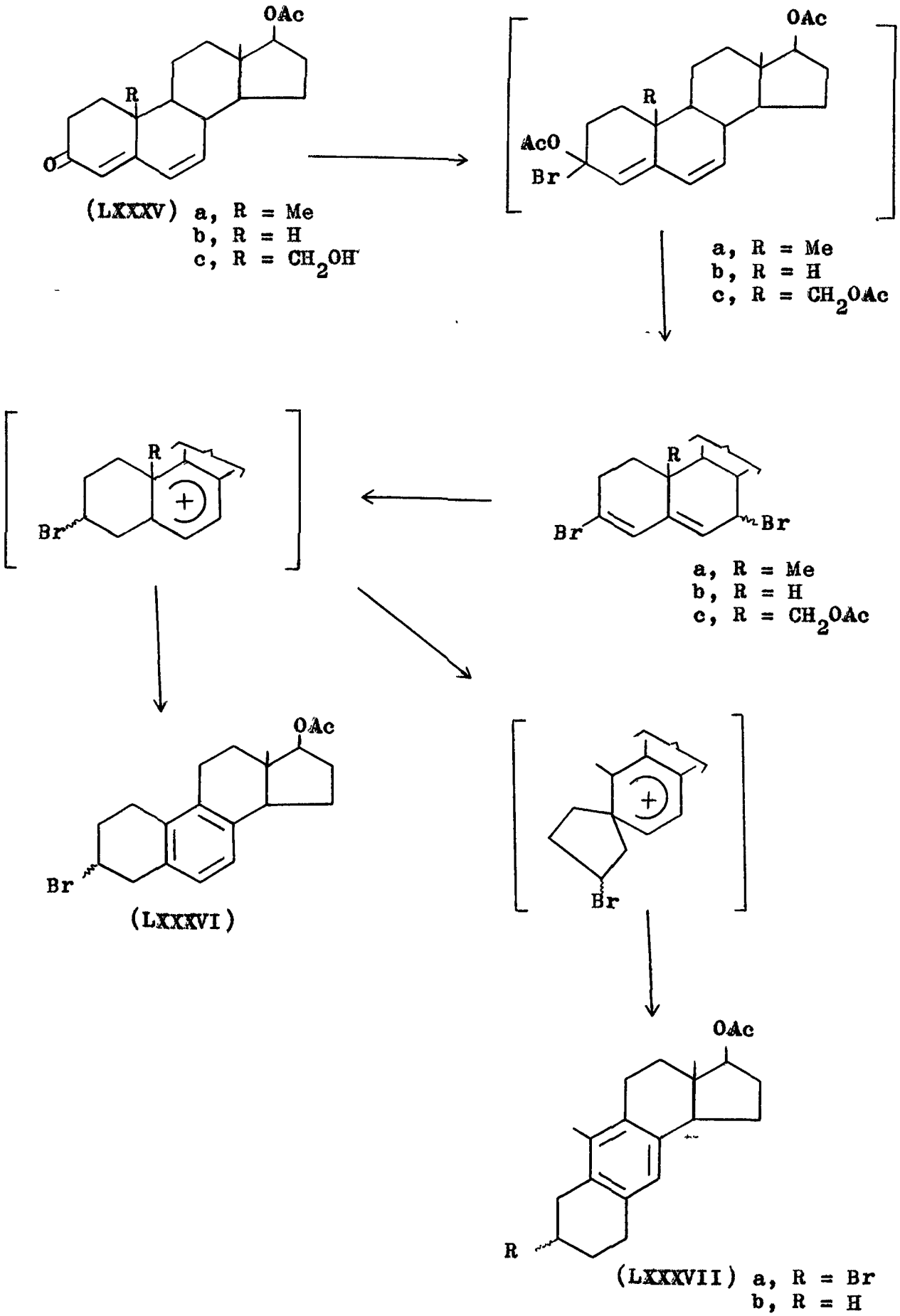
Tsuda et al.[95], and Bladon[96] reported that the dienone-phenol rearrangement of 7-keto- $\Delta^{5,8(9)}$-cholestadien-3-β-ol acetate (LXXXIII) with acetic anhydride and sulphuric acid gave a steroidal phenol (LXXXIV).



(LXXXIII)

(LXXXIV)

Steroidal 3-oxo- $\Delta^{4,6}$-dienones (LXXXV), in both 10-methyl and 19-nor series, readily underwent aromatization with acetyl bromide at room temperature: the former rearrange to anthrasteroids (LXXXVII), while the latter give ring B-aromatic steroids (LXXXVI).



(LXXXV) a, R = Me
b, R = H
c, R = CH_2OH

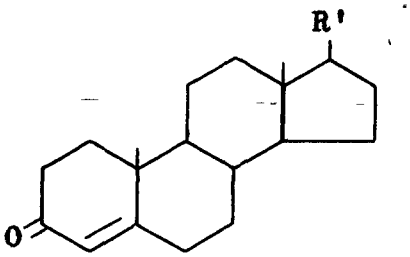
a, R = Me
b, R = H
c, R = CH_2OAc

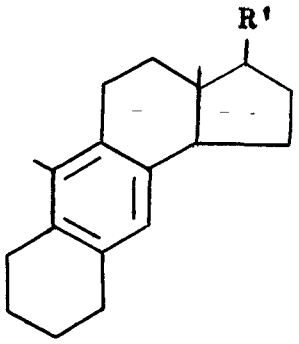
a, R = Me
b, R = H
c, R = CH_2OAc

(LXXXVI)

(LXXXVII) a, R = Br
b, R = H

Steroidal 4-en-3-ones, such as, (LXXXVIIIa) and (LXXXVIIIb) containing two potential sites of unsaturation in rings A and B underwent rearrangement to anthrasteroids (LXXXIXa) and (LXXXIXb) on treatment with acetyl bromide and hydrogen bromide.





(LXXXVIII) a. $R' = C_8H_{17}$
b. R'= OAc

(LXXXIX) a. $R' = C_8H_{17}$
b. R' = OAc

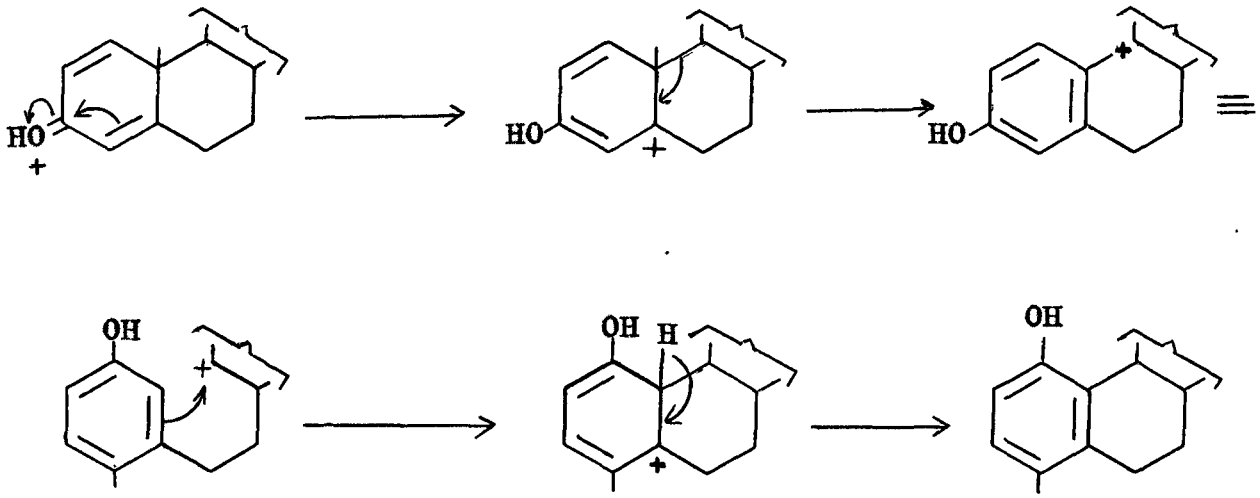
Mechanism

This is an area of carbonium ion chemistry which merits further examination by the physical organic chemist and as an example, there may be offered the observation that the course of the dienone-phenol rearrangement of dienones can proceed in different directions, depending upon the acid medium. No satisfactory explanation has as yet been offered, other than to imply that solvation plays an important role.

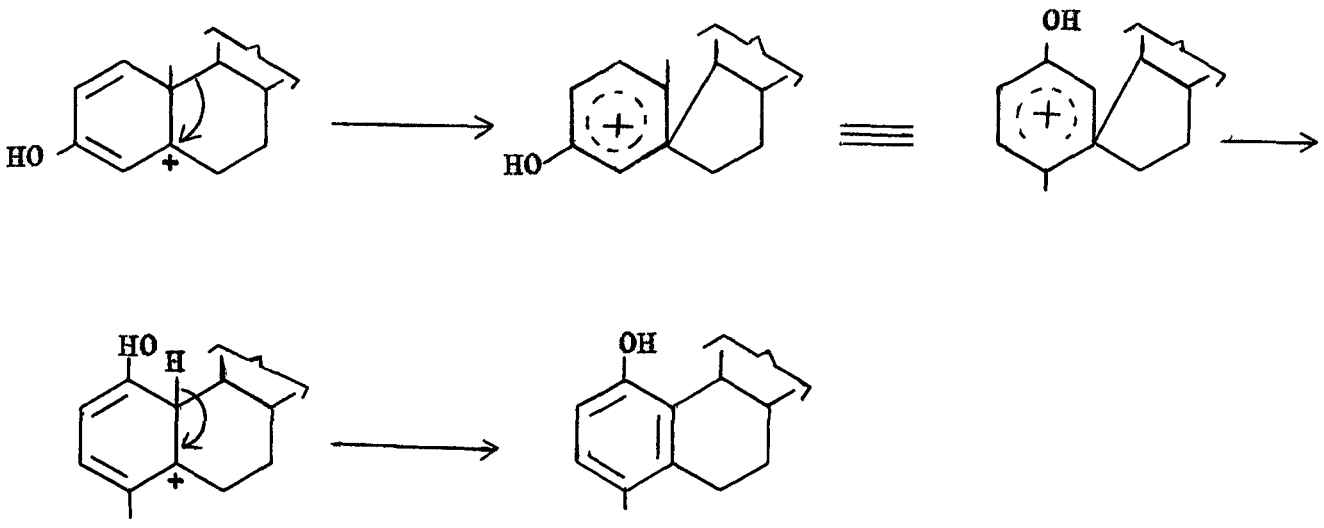
I. The Dienone-Phenol Rearrangement

Since, in general, there are two types of products resulting from the dienone-phenol rearrangement of steroids, numerous rationalizations of the exact mechanisms have been reported in an attempt to explain the anomalous results. However, only three of the most generally accepted paths will be presented.

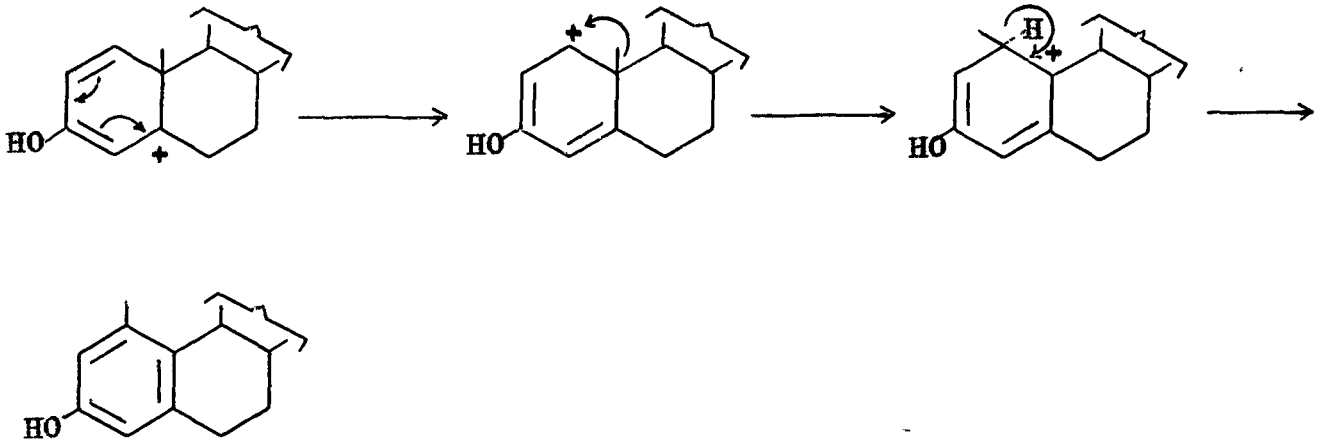
Path A



Path B



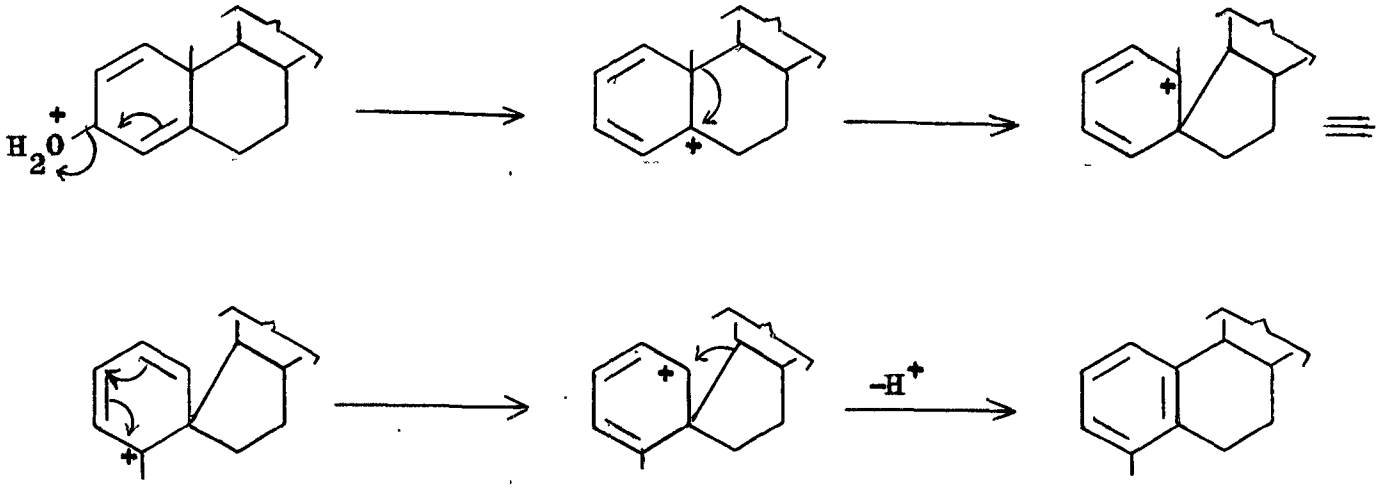
Path C



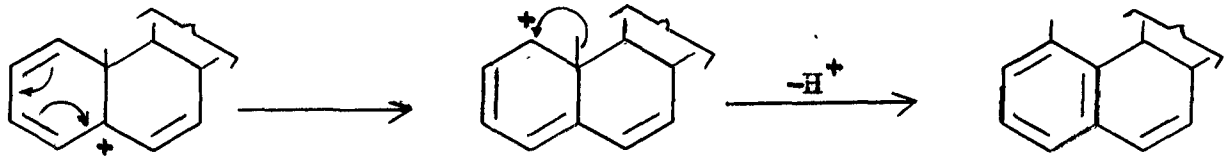
The position of the various functional groups in the steroid, as well as the conditions for the reaction, determine whether the phenol will be of the 'para' type (path a or b) or of the 'meta' type (path c). Any functional group which tends to stabilize the positive charge on the secondary centre (C-1) in preference to that on the tertiary centre (C-5) will lead to a compound of the 'meta' type; conversely, groups which have no influencing effect result in the 'para' type, via the inherently more stable tertiary cation.

II. The Dienol-Benzene Rearrangement

This rearrangement is thought to proceed through a path which is entirely analogous to that of the dienone-phenol rearrangement; the only difference is the loss of water during the incipient stages. The mechanism proceeding via the spiran intermediate is the most generally accepted.



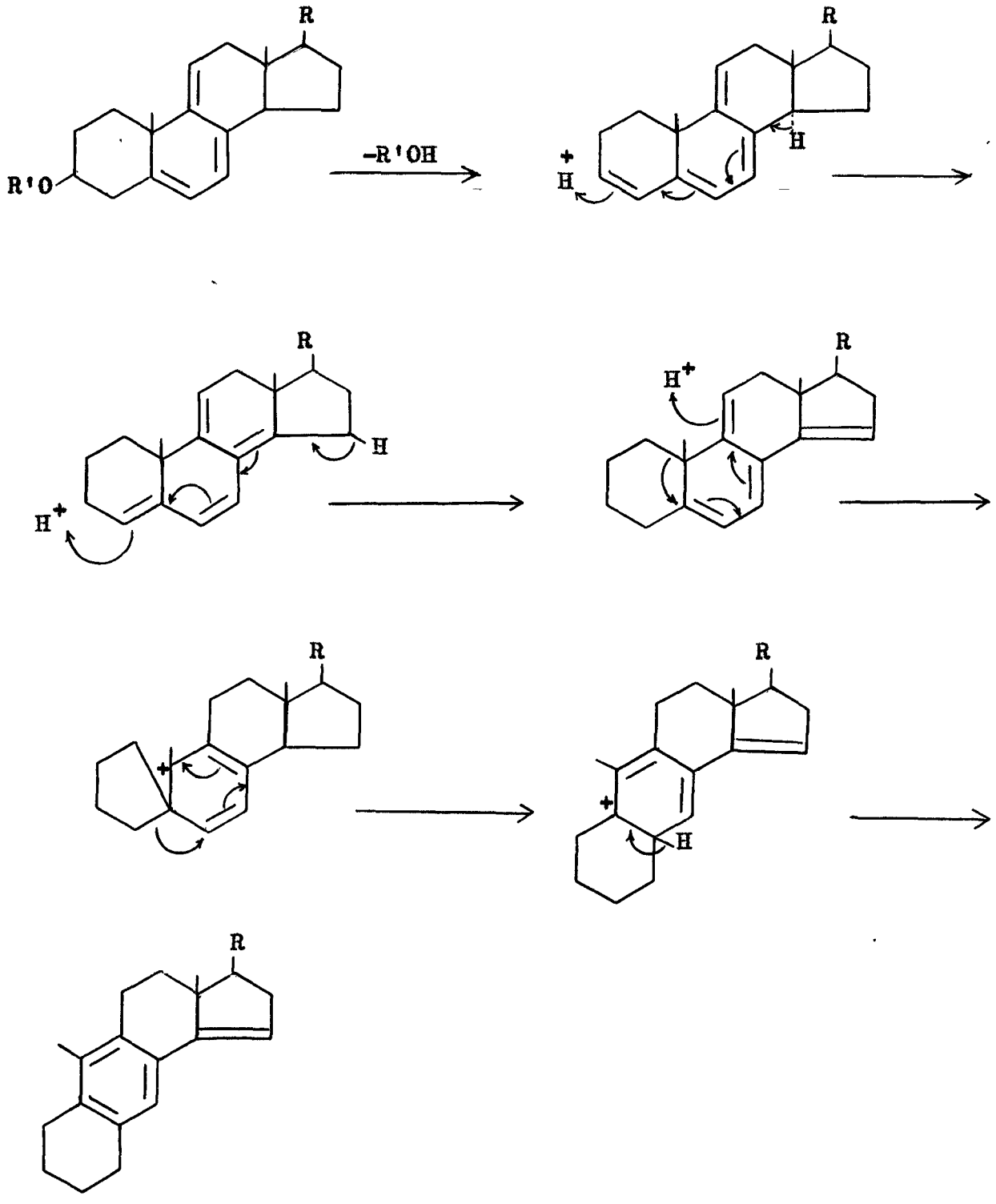
However, when Δ^6-steroid dienones are subjected to the reductive reaction conditions, the conjugation effect comes into play and the resulting product is analogous to a 'meta' type phenol.



III. The Anthrasteroid Rearrangement

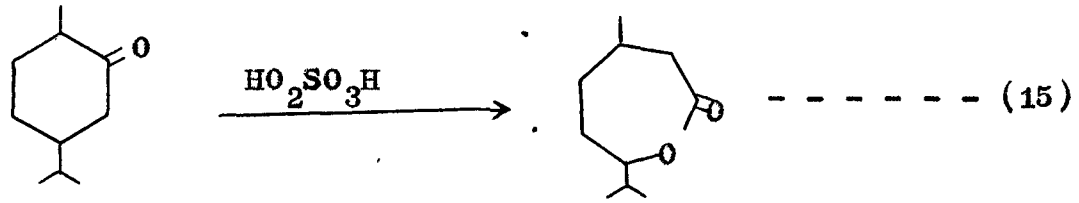
The mechanism for the formation of 5,7,9(11)-trienes is presented here. Compounds containing unsaturation in the B-ring alone result in products with a saturated D-ring by a similar

mechanism. Ring-B dienones proceed by a dienone-phenol rearrangement with migration of C-1.



Baeyer-Villiger Reaction

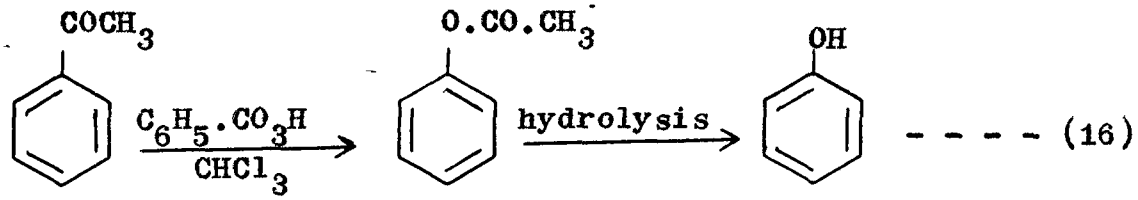
On oxidation with per-acids, ketones are converted into esters or lactones. This reaction was discovered in 1899 by Baeyer and Villiger who found that reaction of a number of alicyclic ketones, including menthone, with Caro's acid (permonosulphuric acid) led to the formation of lactones. For example, menthone gave the lactone (eq. 15).



- - - - - - - (15)

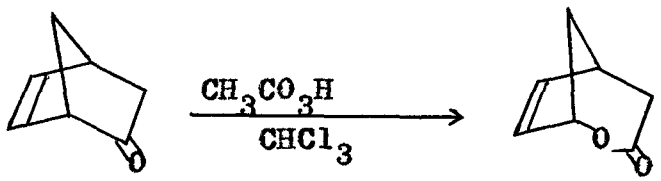
Better yields are obtained with organic per-acids such as per-acetic acid in acetic acid containing sulphuric acid, or one of the stronger per-acids such as permaleic or trifluoroperacetic acid. With the latter acid a buffer such as disodium hydrogen phosphate is often employed to prevent transesterification by the reaction of the newly formed ester with the trifluoroacetic acid always present in the reaction medium. The reaction occurs under mild conditions and has been widely used both in degradative work and in synthesis. It is applicable to open chain and cyclic ketones

as well as to aromatic ketones, and has been used to prepare a variety of steroidal and terpenoid lactones, as well as medium and large ring lactones which are otherwise virtually unobtainable. It also provides a route to alcohols from ketones, by hydrolysis of the esters formed (eq. 16).



- - - - (16)

With unsaturated ketones Baeyer-Villiger reaction often takes place in preference to oxidation of the double bond, with formation of an unsaturated lactone (eq. 17).



(56%) - - - - (17)

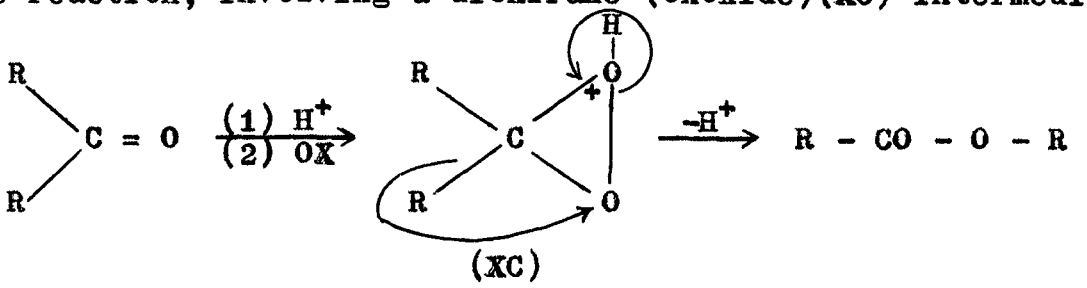
Mechanism:

It was established by Turner[99] on the basis of stereochemical studies that the Baeyer-Villiger rearrangement is an intramolecular process and an optically active group migrates with complete retention of configuration. A number of mechanisms

have been proposed for the Baeyer-Villiger reaction of simple ketones.

I. Baeyer's Mechanism

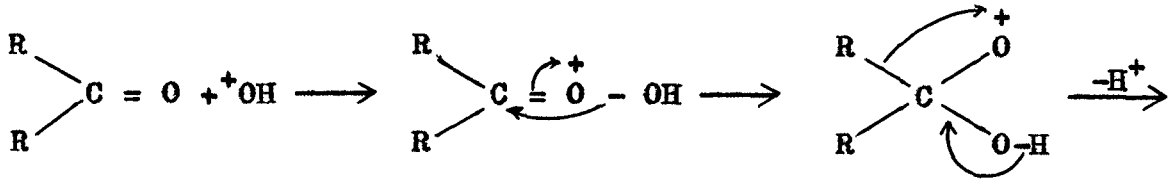
Baeyer and Villiger[100] were first to suggest a path for the reaction, involving a dioxirane (oxoxide)(XC) intermediate.



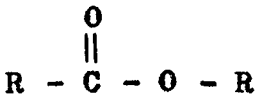
(XC)

II. Wittig's Mechanism

The mechanism proposed by Wittig and Pieper[101] postulates the initiation of reaction with the addition of hydroxy cation to a ketone to give a linear peroxide (XCI). This then changes to the cation (XCII); the latter rearranges to give the product (ester).



(XCI) (XCII)

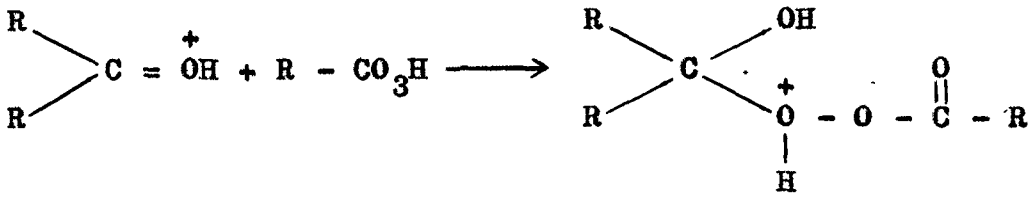


A similar mechanism was also suggested by Treibs[102] and Boeseken[103].

III. Criegee's mechanism

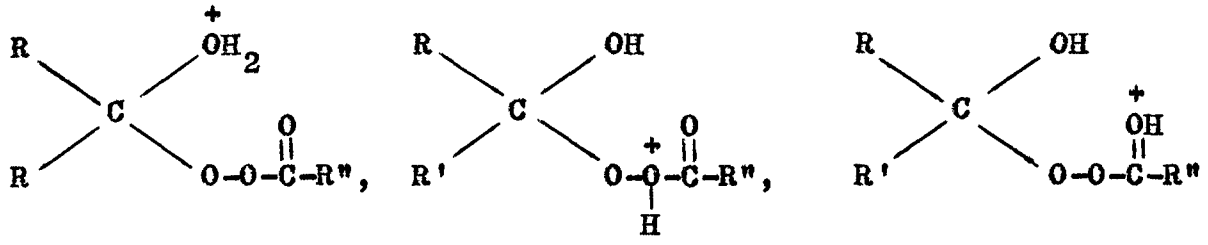
Criegee[104] by analogy of rearrangement of esters of decalin hydroperoxide, suggested the following mechanism which was extended by Friess[105].

The acid-catalysed nucleophilic addition of peroxy acid to the protonated carbonyl group gives an intermediate adduct called Criegee's intermediate (XCIII).



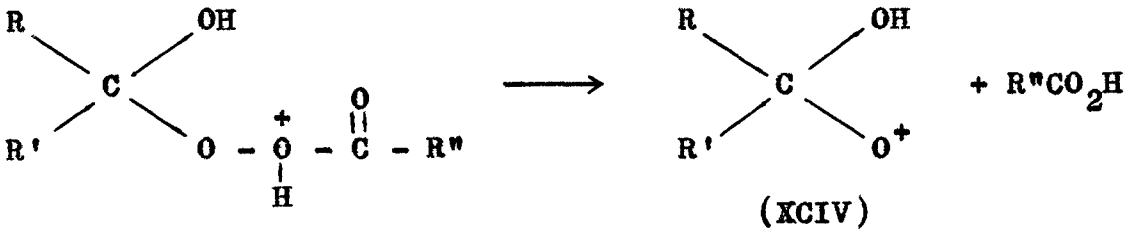
(XCIII)

Subsequently the cleavage of oxygen-oxygen bond of the intermediate adduct takes place homolytically or heterolytically according to the conditions of the reaction. Criegee's mechanism envisages the operation of heterolytic cleavage. This view is supported by the general acid-catalysis of this reaction. Rearrangement of the Criegee's intermediate with simultaneous heterolytic cleavage of oxygen-oxygen bond by concerted process is unlikely because it would involve separation of an anion from an already positively charged site. There are three tautomeric conjugate acids (A), (B) and (C) of Criegee's intermediate.



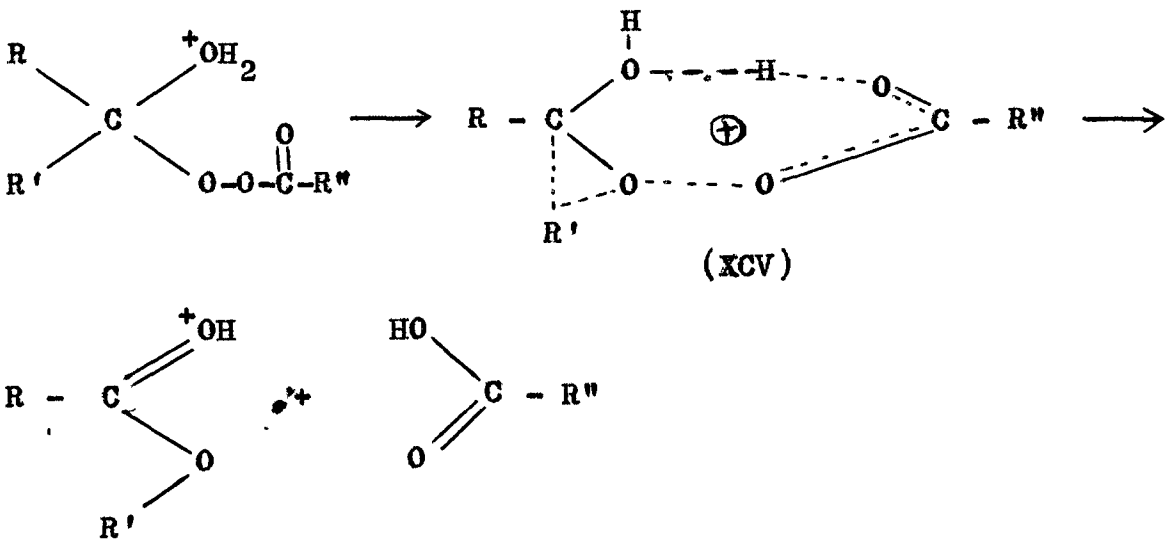
(A) (B) (C)

The cleavage to tautomers B and C may give rise to hydroxy oxygenated cation (XCIV).



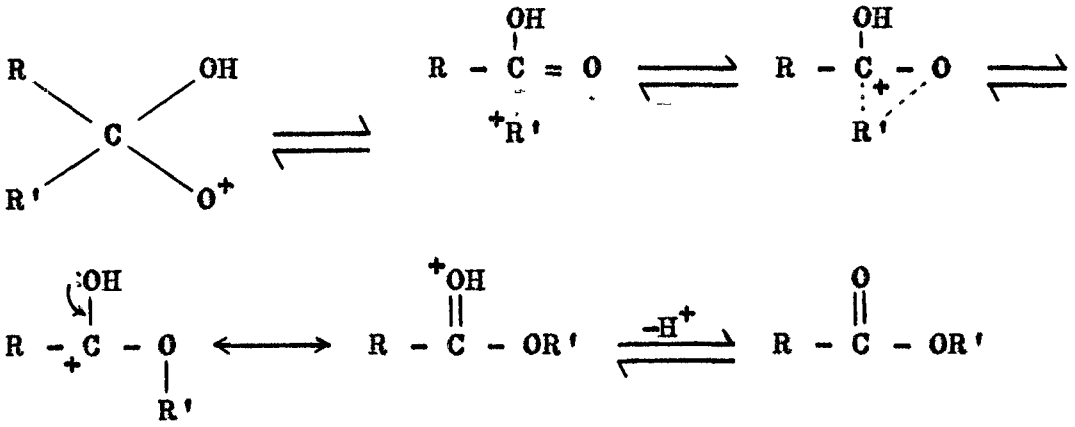
(XCIV)

However, in the case of trifluoroperoxyacetic acid the protonation of either of the carboxyl oxygens would be difficult considering the greater strength of trifluoroacetic acid and also the inertness of the analogous trichloroacetic acid to protonation. A cyclic transition state (XCV) is proposed from which the separation of neutral molecule of acid is more plausible.



(XCV)

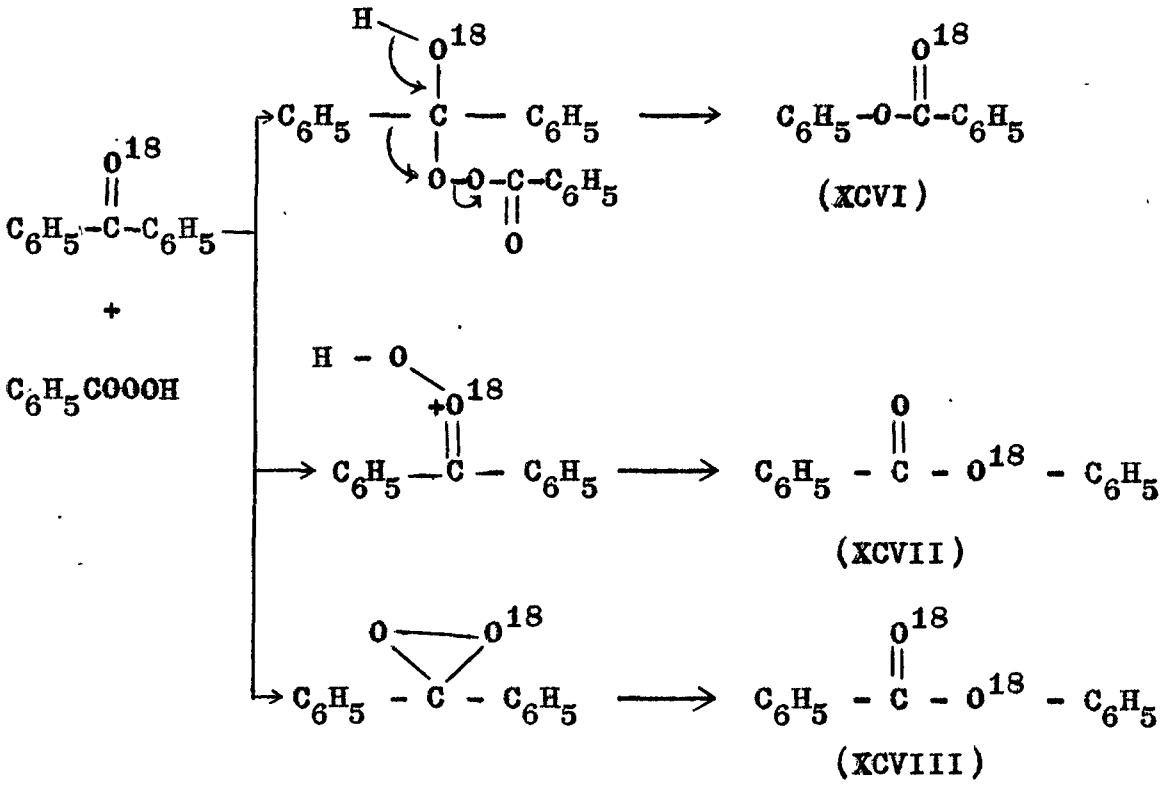
Finally the rearrangement of the hydroxy oxygenated cation intermediate (XCV) results in the formation of the ester. This step involves migration of organic group R from carbon to electrophilic oxygen. As oxygen has higher electron density than carbon, hydroxy oxygenated cation (XCV) may have different forms.



When the potential migrating groups R and R' are different, then there must be two transition states each corresponding to the migration of a group. The lowest energy transition state would correspond to that group that can better accommodate the positive charge to the fully substituted carbon atom. Hence the reaction product distribution will be determined by the degree of substitution of potential migrating group. The steric effect in the group R lowers its energy and also increases the rate of rearrangement. As this rearrangement is SN^1, the intermediate oxygenated cation involves a transition state of pyramidal type.

Most of the ambiguity was dispelled by an experiment by Doering and Dorfman[106] using benzophenone containing isotopically

labelled oxygen and they have concluded that the oxygen of ester carbonyl comes from the ketone. This is in accordance with the Criegee's mechanism. The Baeyer-Villiger oxidation of O^{18} labelled benzophenone gave phenyl benzoate (XCVI), by the shift of phenyl group to adjacent oxygen atom retaining O^{18} with the carbonyl group.

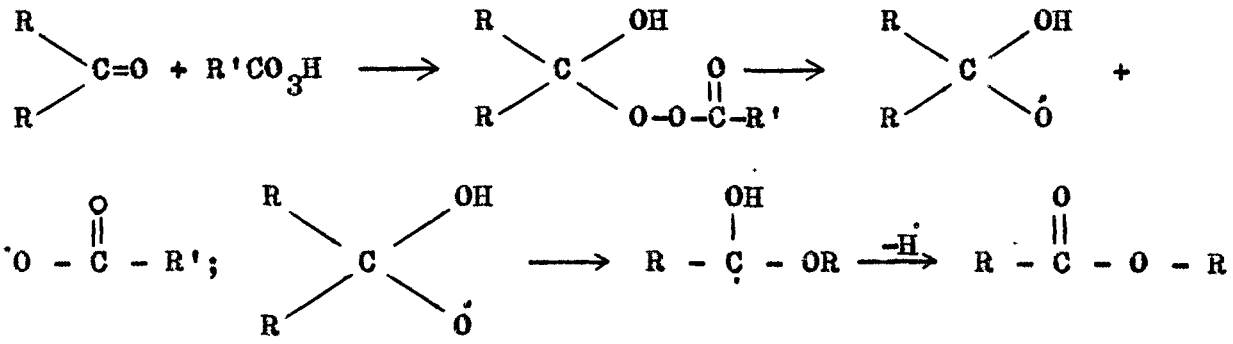


The Wittig's and Treib's mechanisms would, however, lead to the formation of phenyl benzoate ester - O^{18} (XCVII). The Baeyer's mechanism which involves dioxirane intermediate through two equivalent oxygens would lead to equal distribution of isotope of O^{18} between the two oxygen atoms of the ester (XCVIII). Thus this important result ruled out Wittig's, Treib's and Baeyer's

reaction paths and established the validity of Criegee's mechanism.

IV. Free Radical mechanism

After the initial stage of the addition of peroxy compound to the ketone to form intermediate adduct, the cleavage of the adduct may also take place homolytically especially in the presence of light and relatively weak peroxy acids. Thus oxygen-oxygen bond would be cleaved into oxygen radical. Robertson and Swelim[107] envisaged the following free radical mechanism.



When peroxyacetic acid is used as an oxidant, the smaller inductive effect of methyl group favours homolytic cleavage and leads to free radical mechanism. The order of migration in peroxyacetic acid is as given below:

$$H \langle Cl \langle Br \langle NO_2 \langle CH_3 \langle OH \langle OCH_3$$

Such an order of migration is also observed in other free radical rearrangements.

The Kinetics

The detailed kinetic study of this reaction has been made by Friess and Soloway[108]. They observed that ketones with electron-attracting groups showed first order kinetics and those with electron-donating groups showed second order kinetics. Hawthrone and Emmons[109] established a third order kinetics for this reaction and this required the transition state to be derived from all the three reactants.

$$R = K\ (\text{ketone})(\text{Peroxy compound})\ (\text{acid})$$

The rate determining step of this reaction may be either the formation or rearrangement of the adduct. If addition to carbonyl group were the rate determining step then the weaker peroxy acid being more nucleophilic will add faster and if rearrangement were the rate determining step, then stronger acid would give the faster reaction because it could more readily sustain the negative charge developed by the heterolytic cleavage of oxygen-oxygen bond. Experimentally it has been found that the rate constant with peroxyacetic acid is only 1/200 of that found with trifluoroperoxyacetic acid. Hence this difference in rate constants is only accountable by taking rearrangement as the rate determining step for reactive aliphatic ketones. However, ketones which are less reactive towards addition may show a transition towards addition as the rate determining step.

Migratory aptitude

Robertson and Swelim[107] have shown that relative migratory aptitude of groups varied with peroxy acid used. Migratory aptitude of substituted phenyl in Baeyer-Villiger reaction of a series of p,p'-unsymmetrically substituted benzophenones were obtained and are recorded in Tables (III) and (IV).

TABLE - III

Relative migratory aptitude of p-substituted phenyl group (trifluoroperoxyacetic acid as the oxidant)

p-substituent	Migratory aptitude	p-substituent	Migratory aptitude
NO_2	1.00	Br	13.94
t-Butyl	7.93	CH_3	26.05
Cl	12.15	CH_3O	251.00

TABLE - IV

(Peroxyacetic acid as oxidant)

p-substituent	Migratory aptitude	p-substituent	Migratory aptitude
H	1.00	CH_3	8.83
Cl	1.22	OH	26.90
Br	2.14		
NO_2	3.20		

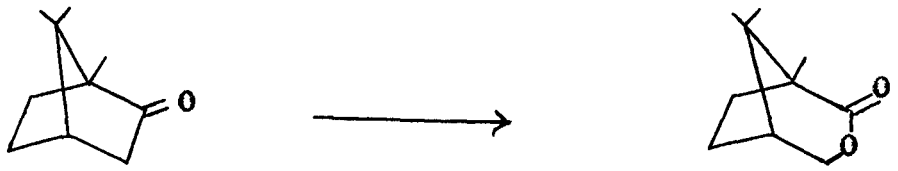
The order of preference for migration among alkyl groups may be listed as below:

Tertiary $\rangle$ Secondary $\rangle$ Primary $\rangle$ Methyl

Yukawa and Yokoyama[110] also concluded that most bulky group which is conformationally trans to the leaving carboxyl group migrates preferentially. The ortho, para-directing groups accelerate the reaction but the meta-directing substituents have opposite effect.

Steric effects

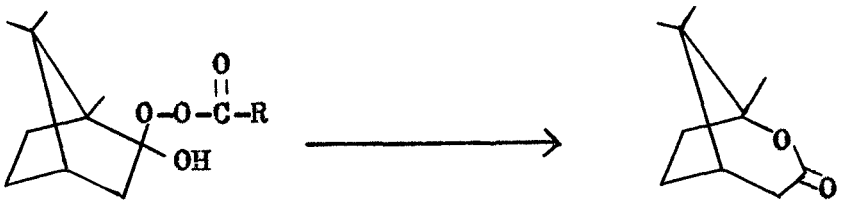
It has been found that in the case of bicyclic ketones, steric effect operates and the relative migratory aptitude is changed. Thus Baeyer and Villiger[100] observed that oxidation of camphor (XCIX) with monoperoxysulphuric acid gave α-campholide (C) due to the preferential migration of primary group (methylene).



(XCIX) (C)

Sauers[111] oxidised camphor with peroxyacetic acid in buffered solution and found that another isomeric lactone (CII) was also obtained.

(CIa) (C)



(CIb) (CII)

The product from Caro's acid is determined by rate limiting addition reaction because the rearrangement step is faster by reason of the greater anionic stability of the leaving sulphate group.

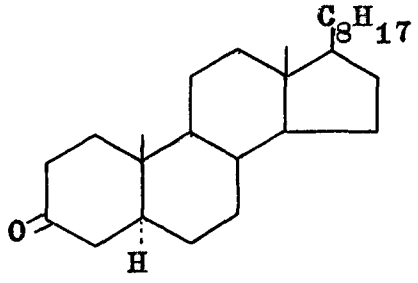
In the case of peroxyacetic acid the product is determined by rate limiting rearrangement. The smaller size of acetate group causes greater stretching of the oxygen-oxygen bond in the transi-

tion state and this reduces the steric compression. The electronically favoured bridge-head migration therefore, takes place through the chair form transition state derived from the adduct (CIb).

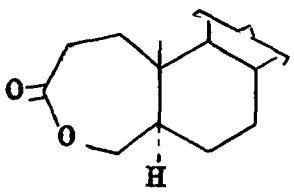
Baeyer-Villiger Oxidation of Steroidal Ketones

Several papers dealing with peracid oxidation of steroidal ketones have appeared recently. These included saturated ketones with carbonyl function located at different positions and α,β-unsaturated ketones, specially pertaining to rings A and B. A wide variety of products, specially from α,β-unsaturated ketones have been obtained from these reactions, the nature and composition of products depending largely upon the oxidant used, its concentration, catalyst and the reaction period.

Ellis and Gardner[112] have shown that 5α-cholestan -3-one (CIII) on heating with ammonium persulphate and aqueous acetic acid furnished 4-oxa-A-homo-5α-cholestan-3-one (CIV) and 3-oxa-A-homo-5α-cholestan-4-one (CV).

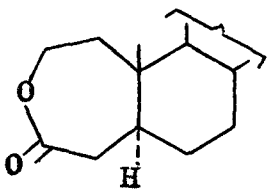


(CIII)



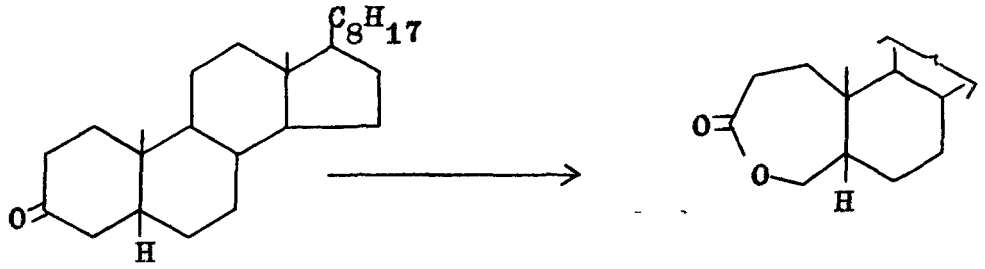
(CIV)

+



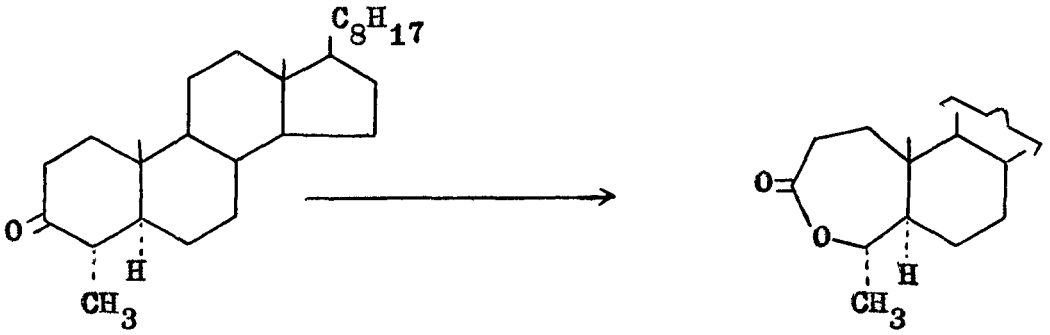
(CV)

But the 5β-analogue (CVI) is reported to give only the 4-oxa-3-keto compound (CVII) from the reaction with ammonium persulphate and acetic acid[113].

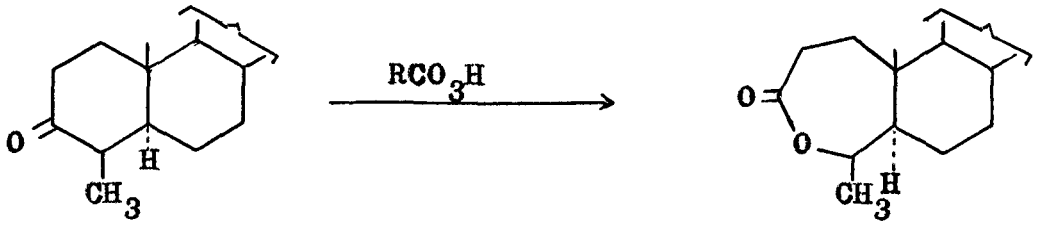


(CVI) (CVII)

Baeyer-Villiger oxidation of 4α- and 4β-methyl cholestanones (CVIII) and (CIX) with m-chloroperbenzoic acid gave as the sole isolable products, the lactones (CX) and CXI), respectively[114] formed by migration of the more highly substituted carbon atom.

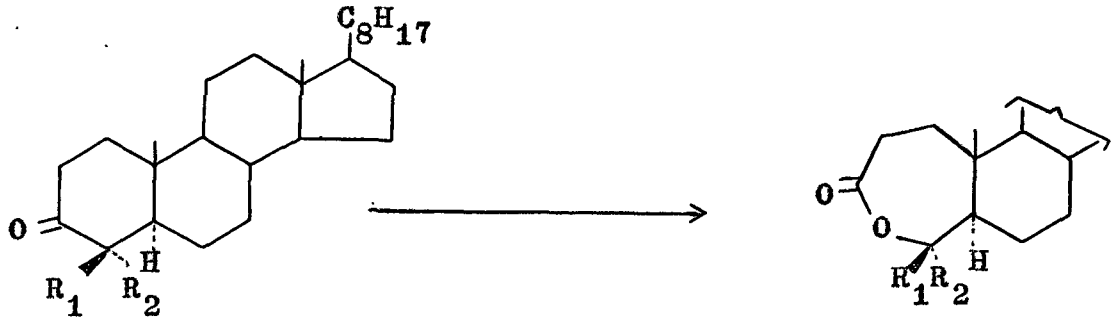


(CVIII) (CX)



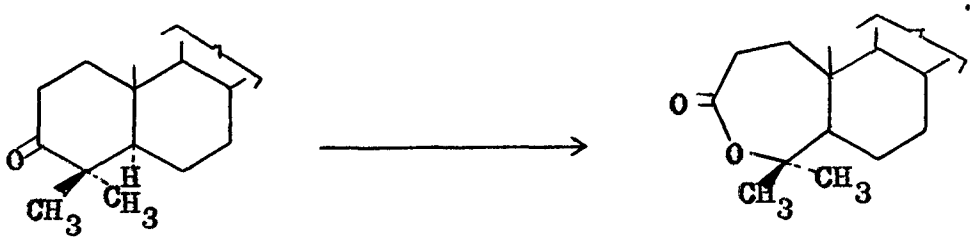
(CIX) (CXI)

Oxidation of 4,4-dimethylcholestan-3-one (CXII) with peroxyacid in the presence of mineral acid gave the unexpected lactone, 4aα-methyl-4-oxa-A-homo-5α-cholestan-3-one (CX)[115], where the loss of one methyl group occurred.



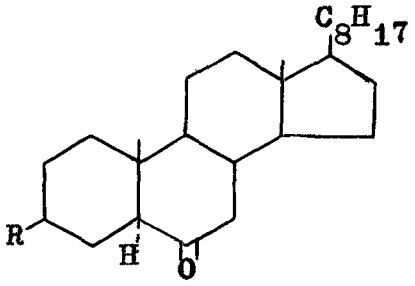
(CXII) $R_1, R_2 = CH_3$ (CX) $R_1 = H$, $R_2 = Me$

In the absence of mineral acid, oxidation of (CXII) with peroxyacid gave the expected lactone (CXIII) without the loss of a methyl group which was shown to arise by cleavage between C_3 and C_4 bond.

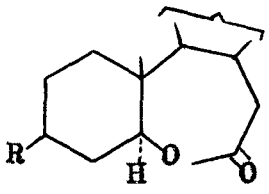


(CXII) (CXIII)

When 5α-cholestan-6-one (CXIV) and its 3β-acetoxy derivative (CXV) were allowed to react with perbenzoic acid the corresponding lactone (CXVI) and (CXVII)[116] were obtained.

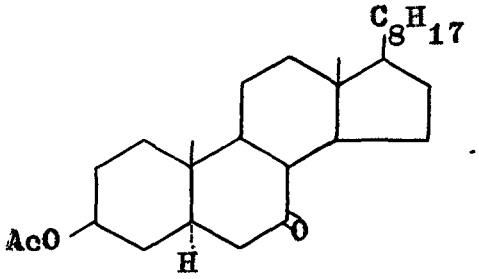


(CXIV) R, H
(CXV) R, OAc

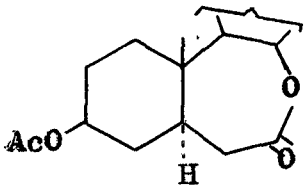


(CXVI) R, H
(CXVII) R, OAc

Baeyer-Villiger oxidation of 3β-acetoxy-5α-cholestan-7-one (CXVIII) with peroxybenzoic acid gave a single product, 3β-acetoxy-7a-oxa-B-homo-5α-cholestan-7-one (CXIX)[117].

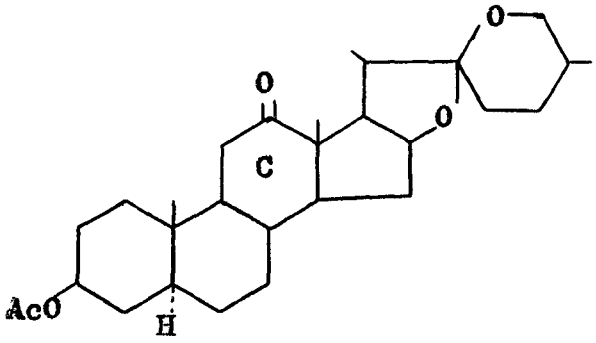


(CXVIII)

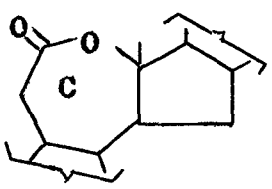


(CXIX)

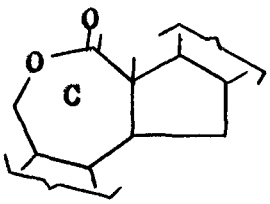
Baeyer-Villiger oxidation of hecogenin acetate (CXX) with peracetic acid and perbenzoic acid in the presence of sulphuric acid as the catalyst provided a mixture of the lactones (CXXI)[118] and (CXXII)[119].



(CXX)

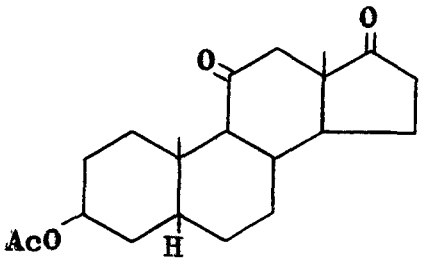


(CXXI)

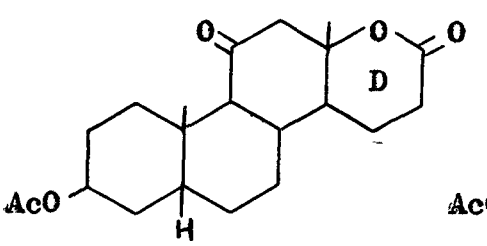


(CXXII)

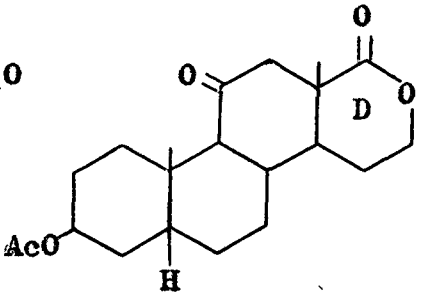
A mixture of ring D-lactones (CXXIV)[120] and (CXXV)[121] was obtained by the oxidation of 3β-acetoxy-5β-androstane-11,17-dione (CXXIII).



(CXXIII)

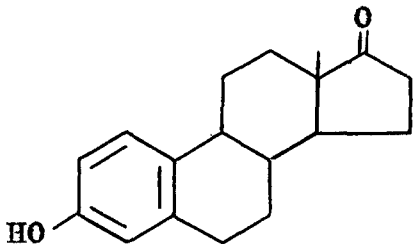


(CXXIV)

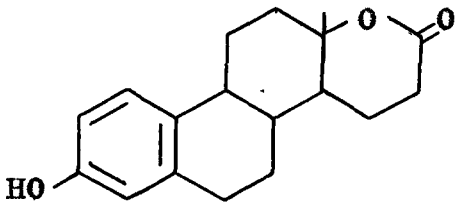


(CXXV)

Oxidation of estrone (CXXVI) with hydrogen peroxide in alkaline solution provided the oestrone lactone (CXXVII)[122].



(CXXVI)

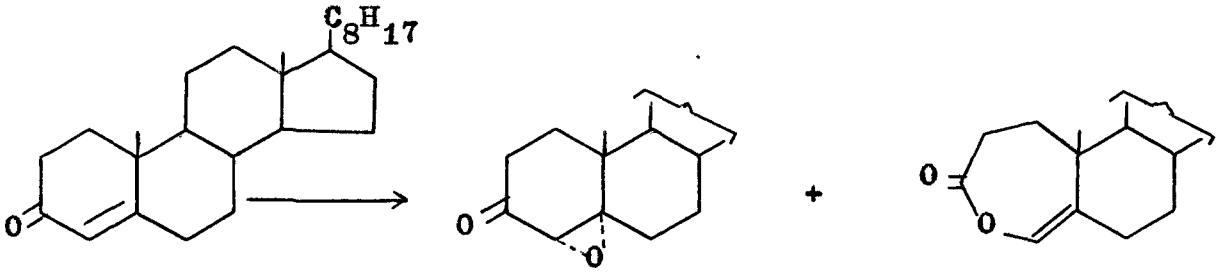


(CXXVII)

Baeyer-Villiger Oxidation of α,β-unsaturated ketones

Peracid oxidation of α,β-unsaturated ketones may, by oxygen insertion between the double bond and the carbonyl group lead to enol esters, epoxy esters and epoxy ketones[123-126]. However, peracid oxidation of Δ^4-3-ketosteroids may result in an even larger variety of products depending upon the reaction conditions and the peracid used.

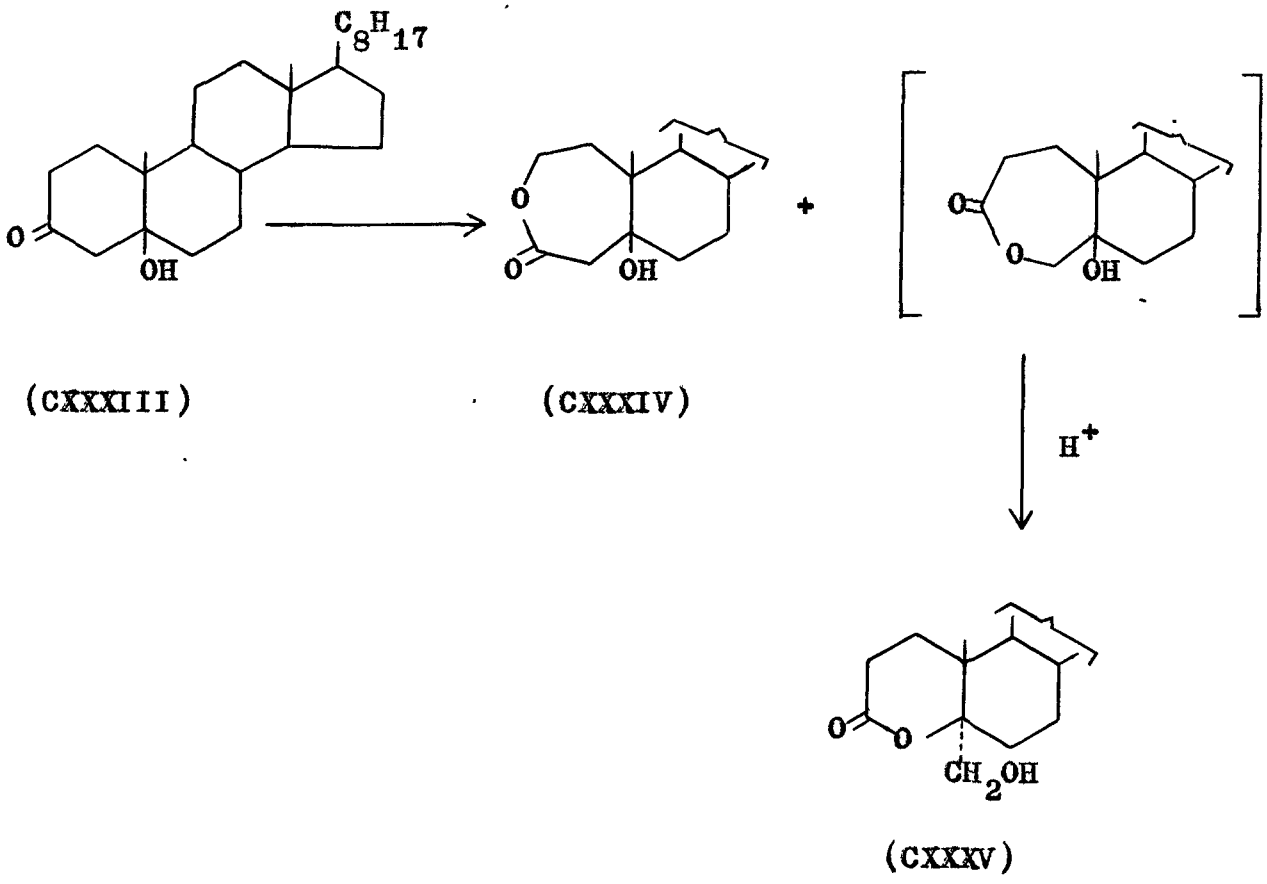
The action of perbenzoic acid in the presence of anhydrous perchloric acid on cholest-4-en-3-one (CXXVIII) yielded four products established as 4α,5-epoxy-5α-cholestan-3-one (CXXIX), 4-oxa-A-homocholest-4a-en-3-one (CXXX), 5-formyl-4-oxa-5α-cholestan-3-one (CXXXI) and 3,5-seco-4-norcholestan-5-one-3-oic acid (CXXXII)[127], together with some unchanged starting material.



(CXXVIII) (CXXIX) (CXXX)

(CXXXI) (CXXXII)

Trifluoroperacetic acid oxidation of 5-hydroxy-5β-cholestan-3-one (CXXXIII) followed by chromatography of the product on alumina gave 5-hydroxy-3-oxa-A-homo-5β-cholestan-4-one (CXXXIV, 20%) and 5-hydroxymethyl-4-oxa-5α-cholestan-3-one (CXXXV, 40%). These lactones had spectra consistent with the assigned structures and were recovered unchanged after alkaline hydrolysis followed by acid treatment[127].

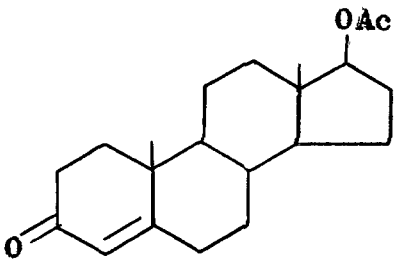


(CXXXIII) (CXXXIV)

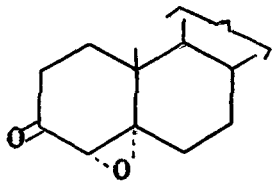
(CXXXV)

Baeyer-Villiger oxidation of testosterone acetate (CXXXVI) with perbenzoic acid and m-chloroperbenzoic acid in the presence of

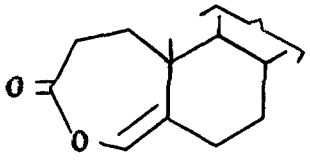
perchloric acid as the catalyst was carried out by Mazur et al.[128] They explained that the relative amounts of products depend upon the duration of reaction, peracid used, its concentration and catalyst. When testosterone acetate (CXXXVI) was treated with (1 mole) of perbenzoic acid in the presence of anhydrous perchloric acid for 12 hours, the enol lactone, 17β-acetoxy-4-oxa-A-homo-androst-4a-en-3-one (CXXXVIII) was obtained along with 17β-acetoxy-4α,5α-epoxyandrostan-3-one (CXXXVII) and 17β-acetoxy-5-formyl-4-oxa-5α-androstan-3-one (CXXXIX).



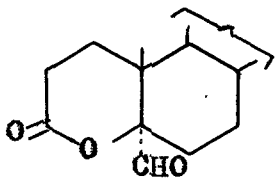
(CXXXVI)



(CXXXVII)



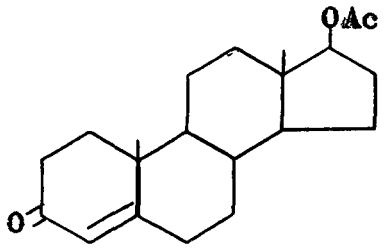
(CXXXVIII)



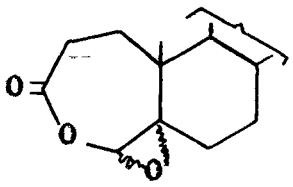
(CXXXIX)

When testosterone acetate (CXXXVI) was allowed to react with 2 moles of perbenzoic acid in the presence of anhydrous perchloric

acid the products obtained were 17β-acetoxy-4α,5-epoxy-4-oxa-A-homoandrostan-3-ones (CXL) and (CXLI), the epoxy ketone (CXXXVII) and methyl 17β-acetoxy-3,5-seco-4-nor-5β-hydroxy-5α-formyl androstan-3-oate (CXLII).

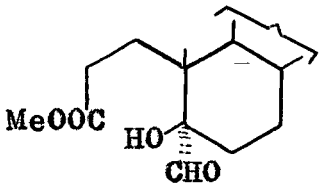


(CXXXVI)

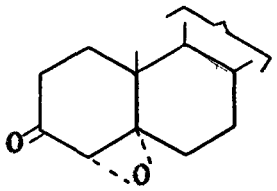


(CXL) 4a,α5α-
(CXLI) 4a,β5β-

+

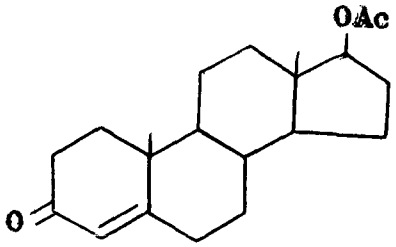


(CXLII)

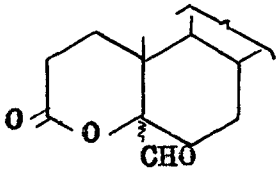


(CXXXVII)

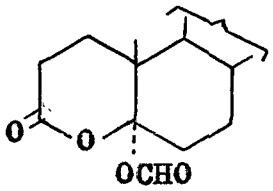
When 4 moles of perbenzoic acid was used with perchloric acid anhydrous as catalyst for 84 hours the products obtained were 5α- and 5β-formyl-δ-lactones (CXXXIX) and (CXLIII), the epoxy lactone (CXLI), the epoxy ketone (CXXXVII) and 17β-acetoxy-5-formate-4-oxa-5α-androstan-3-one (CXLIV).



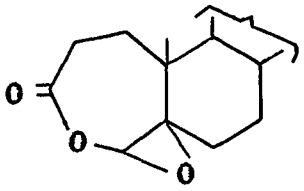
(CXXXVI)



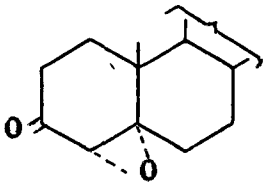
(CXXXIX) - 5α
(CXLIII) - 5β



(CXLIV)

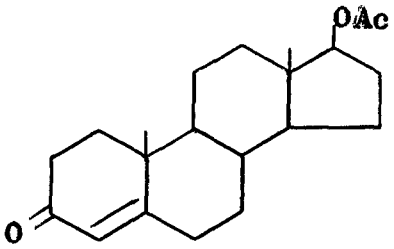


(CXLI)

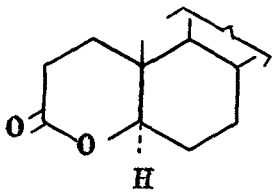


(CXXXVII)

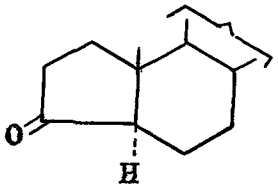
Similar oxidation with perbenzoic acid (2 mole) in the presence of aqueous perchloric acid leads to the δ-lactone (CXLV) and 17β-acetoxy-A-norandrostan-3-one (CXLVI).



(CXXXVI)



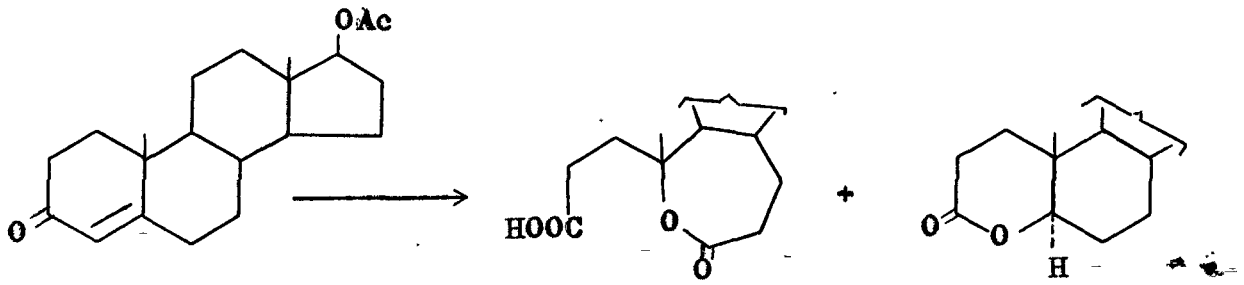
(CXLV)



(CXLVI)

When m-chloroperbenzoic acid was used as the oxidizing agent and aqueous perchloric acid as catalyst, the δ-lactone (CXLV), the A-norketone (CXLVI), the lactone aldehyde (CXXXIX) and 17β-

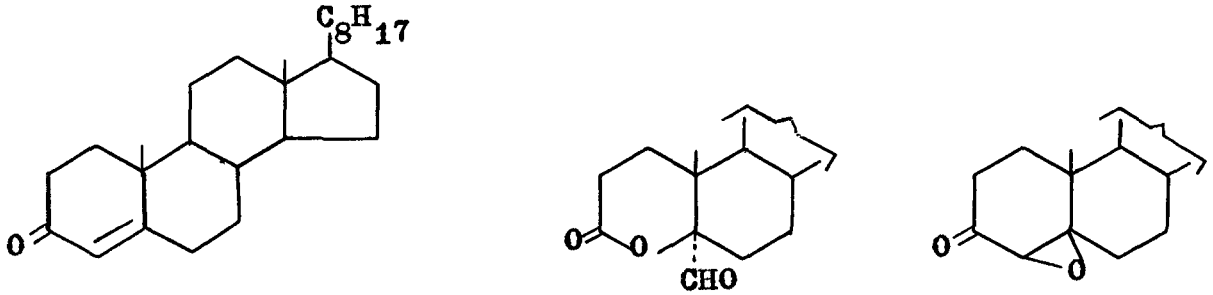
acetoxy-3,5-seco-4-nor-5-oxa-B-homoandrostan-6-one-2-carboxylic acid (CXLVII) were obtained.



(CXXXVI) (CXLVII) (CXLV)

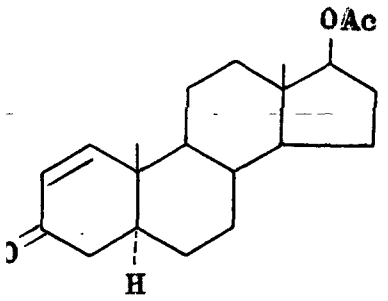
(CXLVI) (CXXXIX)

Finhey and Schaffner[129] carried out the Baeyer-Villiger oxidation of cholest-4-en-3-one (CXXVIII) with trifluoroperoxy acetic acid in buffer solution. They obtained 5-formyl-4-oxa-5α-cholestan-3-one (CXXXI) and 4β,5-epoxy-5β-cholestan-3-one (CXLVIII).

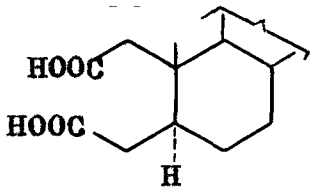


(CXXVIII) (CXXXI) (CXLVIII)

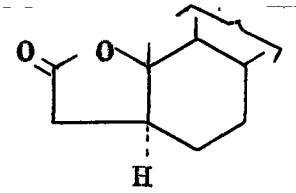
Caspi and Schimizu[130] have reported the Baeyer-Villiger oxidation of 17β-acetoxy-5α-androst-1-en-3-one (CXLIX) with hydrogen peroxide in the presence of selenium dioxide and obtained 17β-acetoxy-2,3-seco-5α-androst-1,4-dicarboxylic acid (CL) and the γ-lactone (CLI).



(CXLIX)

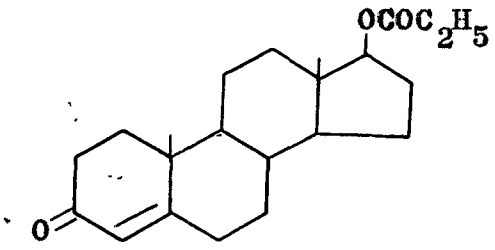


(CL)

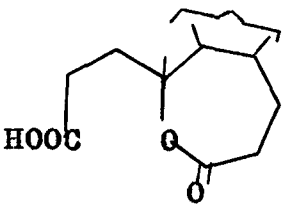


(CLI)

Oxidation of testosterone propionate (CLII) with hydrogen peroxide in the presence of selenium dioxide in t-butyl alcohol gave the ε-lactone carboxylic acid (CLIII) and the γ-lactone acid (CLIV)[131].

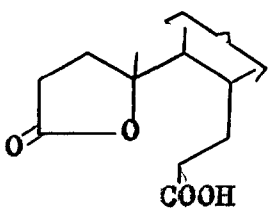


(CLII)



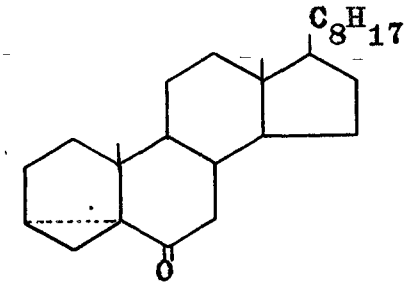
(CLIII)

+

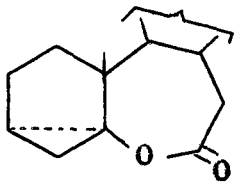


(CLIV)

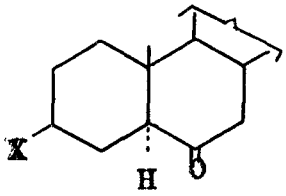
Ahmad et al.[132] have reported the Baeyer-Villiger oxidation of 3α,5-cyclo-5α-cholestan-6-one (CLV) and its 3β-halo derivatives, 3β-chloro (CLVII), 3β-bromo (CLVIII) and 3β-iodo (CLIX) 5α-cholestan-6-ones. They obtained the corresponding 6-oxa compounds (CLVI), (CLX), (CLXI) and (CLXII), respectively.



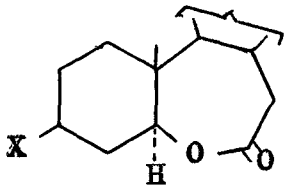
(CLV)



(CLVI)



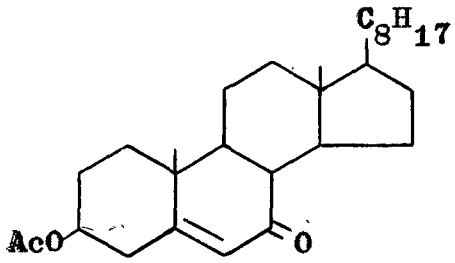
(CLVII) X, Cl
(CLVIII) X, Br
(CLIX) X, I



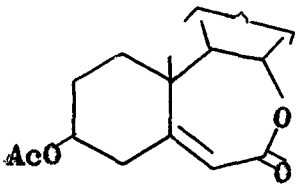
(CLX) X, Cl
(CLXI) X, Br
(CLXII) X, I

They further[133] carried out the Baeyer-Villiger oxidation of 3β-acetoxycholest-5-en-7-one (CLXIII) using perbenzoic acid as the oxidizing agent and p-toluenesulphonic acid as the catalyst, and obtained 3β-acetoxy-7a-oxa-B-homocholest-5-en-7-one (CLXIV),

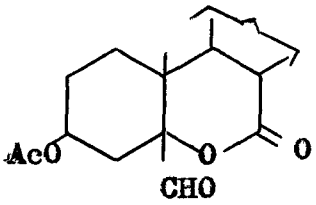
3β-acetoxy-6-oxa-5-formyl-5β-cholestan-7-one (CLXV) and a mixture of the seco acids, 3β-acetoxy-5-keto-5,7-seco-6-norcholestan-7-oic acid (CLXVI) and 5-keto-5,7-seco-6-norcholest-3-en-7-oic acid (CLXVII). The formation of (CLXIV) shows that a more substituted carbon as C8 has at least comparable migratory aptitude with that of a vinylic group.



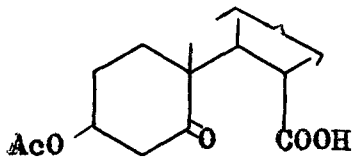
(CLXIII)



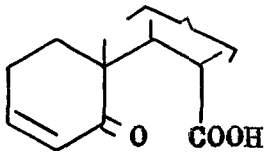
(CLXIV)



(CLXV)



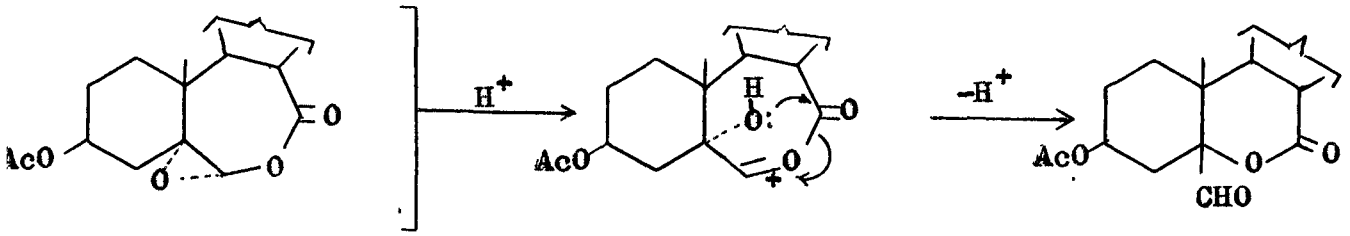
(CLXVI)



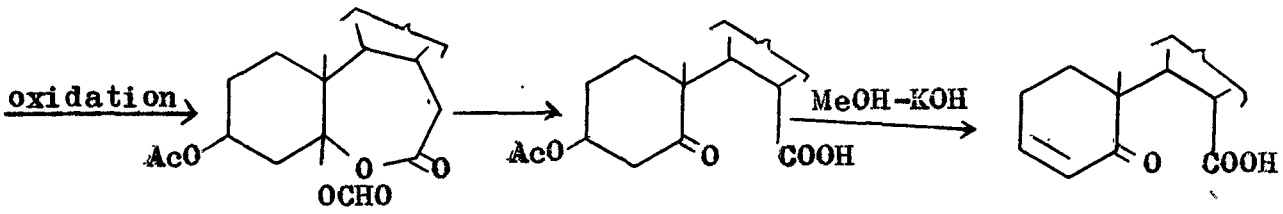
(CLXVII)

The formyl derivative (CLXV) and the seco acids (CLXVI) and (CLXVII) could possibly arise by the acid catalysed rearrangement of the epoxy ∈-lactone intermediate as shown below. The exclusive formation of the 5β-formyl derivative (CLXV) and the absence of its 5α-epimer suggested that the epoxy oxygen in

ϵ-lactone to be α-oriented.

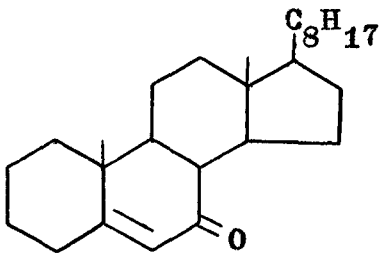


(CLXV)

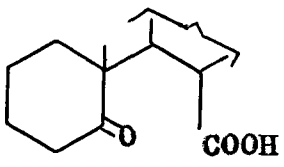


(CLXVI) (CLXVII)

Oxidation of cholest-5-en-7-one (CLXVIII), under similar conditions, gave a single compound, 5-keto-5,7-seco-6-norcholestan-7-oic acid (CLXIX)[133].

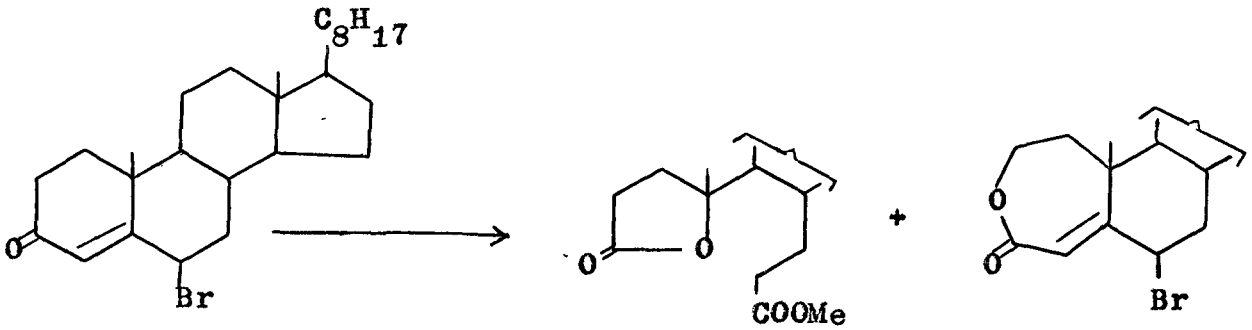


(CLXVIII)



(CLXIX)

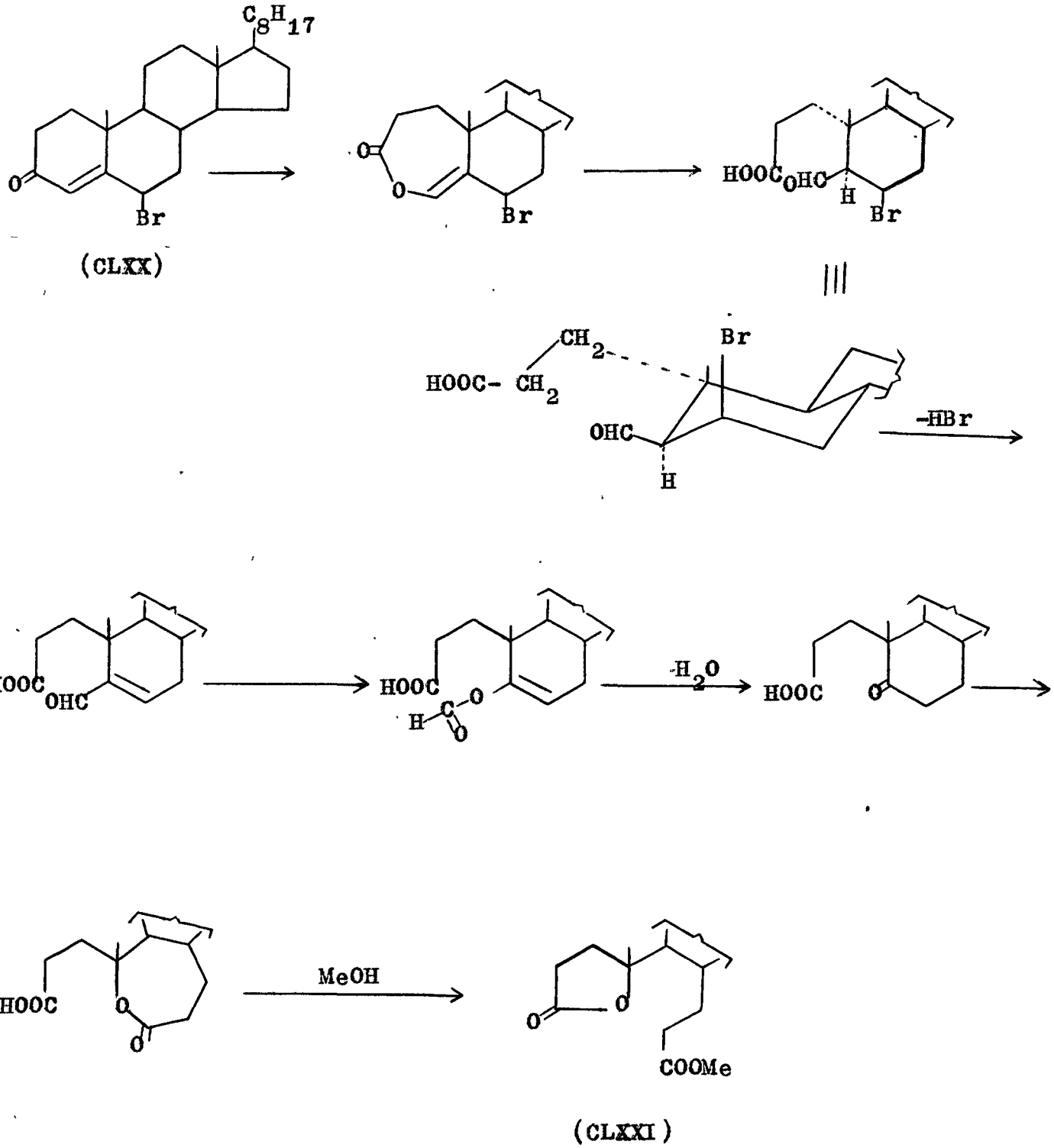
An interesting result reported by Ahmad et al.[134] is that from the Baeyer-Villiger oxidation of 6β-bromocholest-4-en-3-one (CLXX), two compounds were obtained which were characterized as the γ-lactone acid methyl ester (CLXXI) and the ε-lactone (CLXXII).



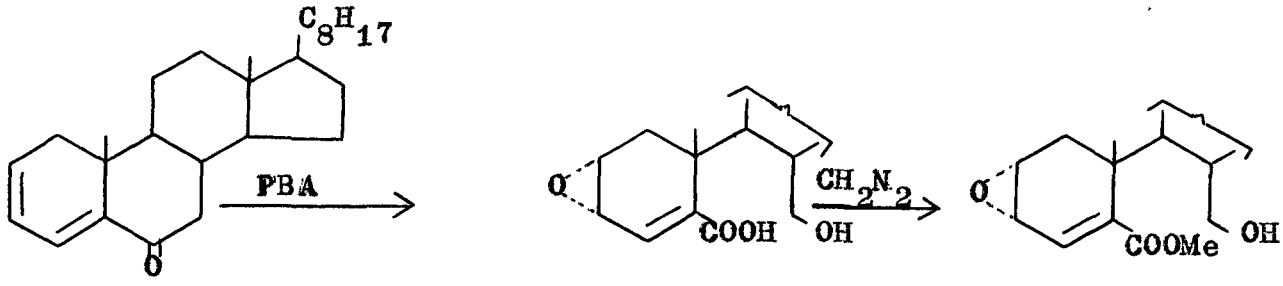
(CLXX) (CLXXI) (CLXXII)

A possible mechanism for the formation of the γ-lactone (CLXXI) from (CLXX) can be shown according to scheme 1, in view of the established routes for Baeyer-Villiger oxidation of unsaturated ketones[134,135].

Scheme - 1

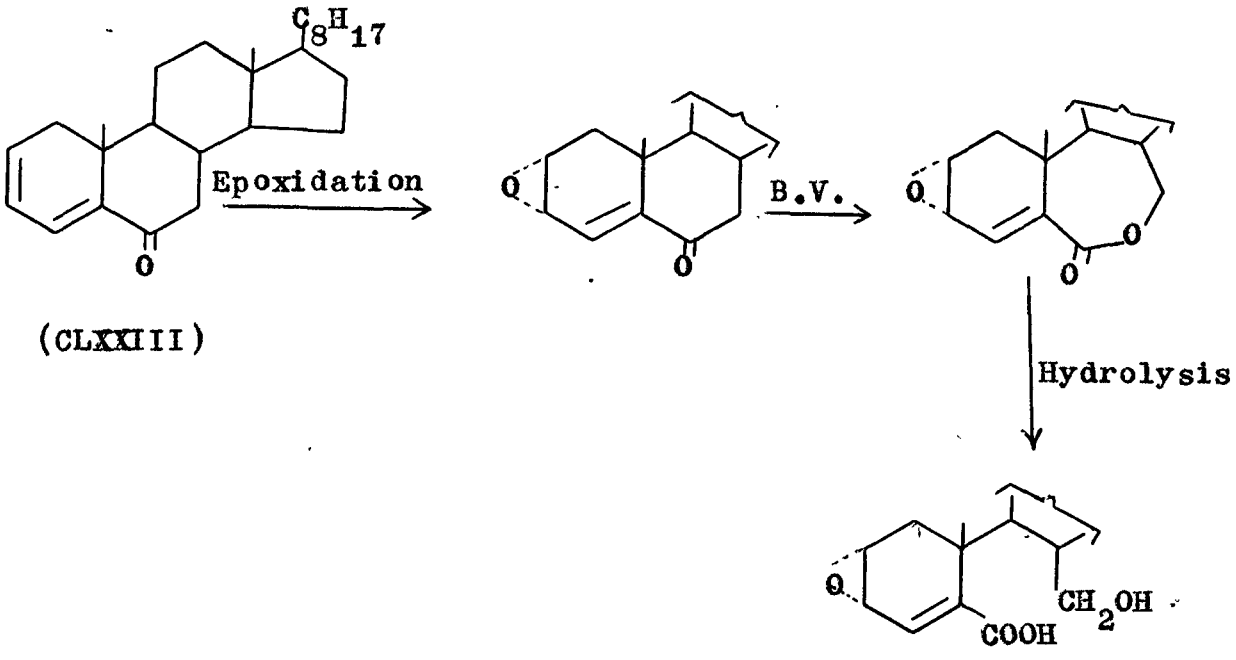

C_8H_{17}
O
Br
(CLXX)
HOOC
OHC
H
Br
CH_2
$HOOC-CH_2$
-HBr
H_2O
MeOH
COOMe
(CLXXI)

The dienone (CLXXIII) on treatment with an excess of perbenzoic acid gave 2α,3α-oxido-5,6-secocholest-4-en-7-ol-5-oic acid (CLXXIV)[136] as the only isolable compound. The structure of (CLXXIV) was established by its spectral properties and conversion of (CLXXIV) to its methyl ester (CLXXV).



(CLXXIII) (CLXXIV) (CLXXV)

The formation of (CLXXIV) from (CLXXIII) can be rationalised according to the following sequence of reactions.

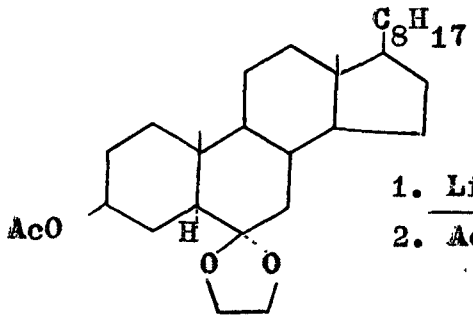


(CLXXIII)

(CLXXIV)

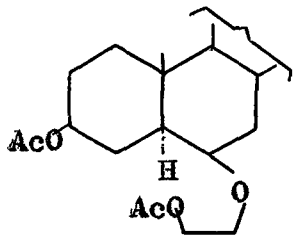
DISCUSSION

Previous work from these laboratories has described the preparation of several steroidal cyclic acetals from the respective ketones and the lithium aluminium hydride - aluminium chloride (1:1; AlH_2Cl) reduction of the former into the corresponding hydroxy ethers. The following chart gives an account of the work carried out in this connection.



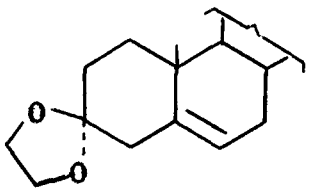
(CLXXVI)

1. $LiAlH_4/AlCl_3$
2. Ac_2O/Py



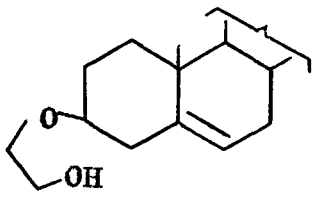
(CLXXVII)

Ref. 62



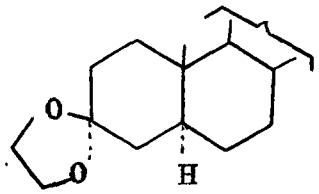
(CLXXVIII)

$LiAlH_4/AlCl_3$

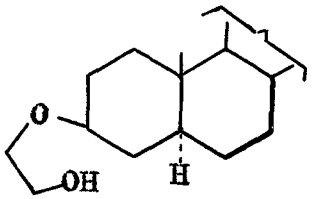


(XXIX)

61

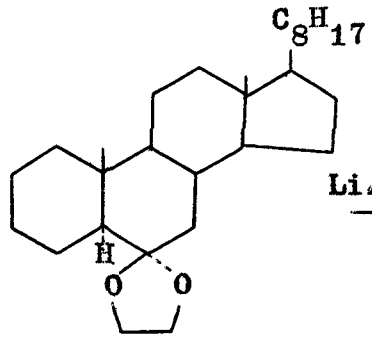


(CLXXIX)

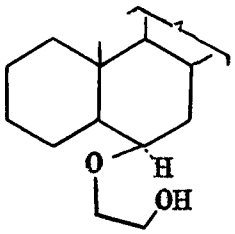


(CLXXX)

61



$LiAlH_4/AlCl_3$



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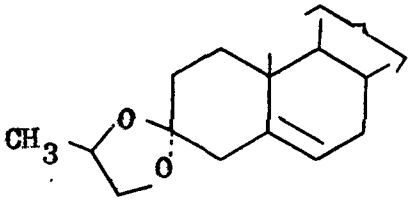
(CLXXXI) (CLXXXII)



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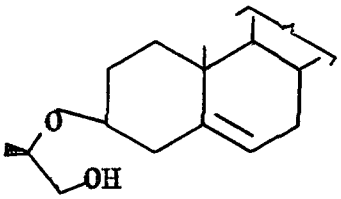

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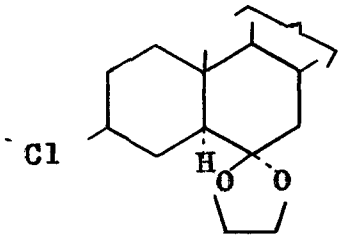
(CLXXXIII) (XXXIII)



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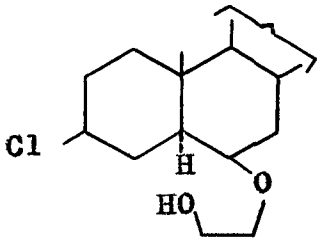

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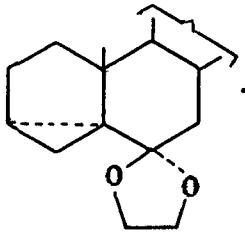
(CLXXXIV) (CLXXXV)



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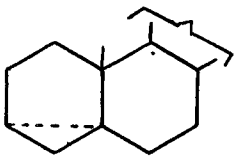

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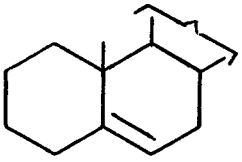
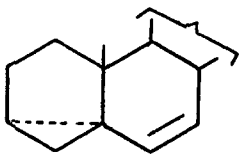


(XXIV) (XXV) (XXVI)



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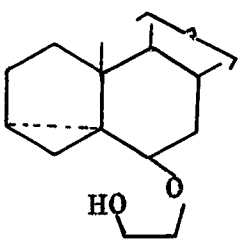

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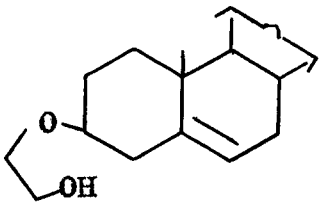
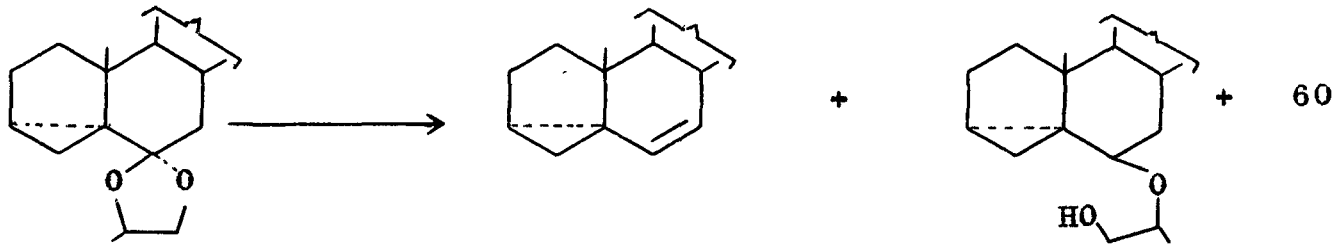
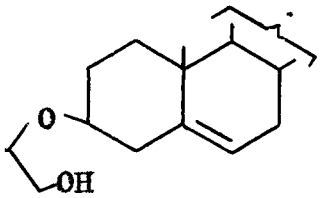


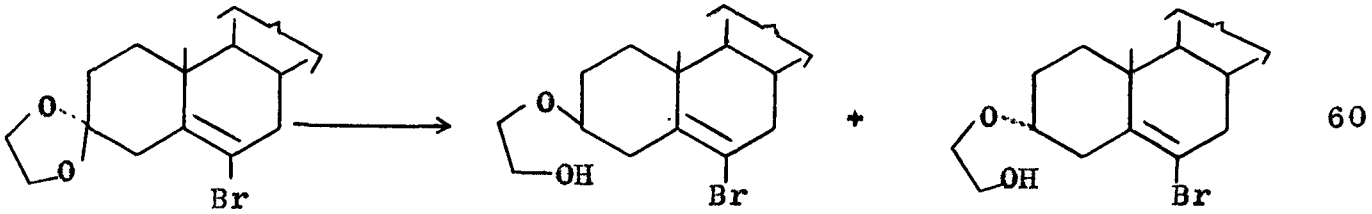
(XXVII) (XXVIII) (XXIX)



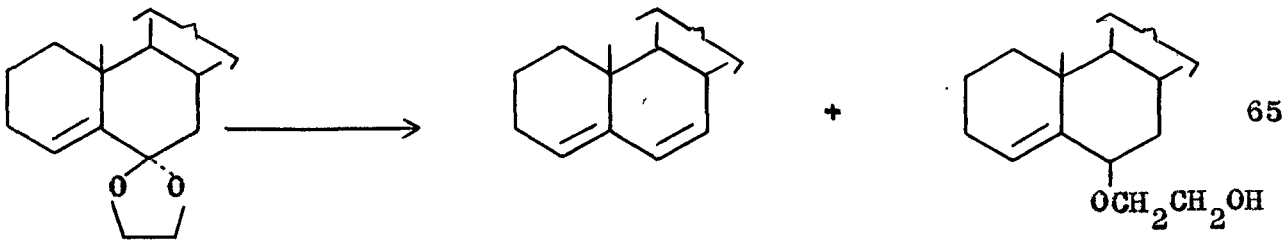
(XXX) (XXVII) (XXXI)



(XXXIII)



(XXI) (XXIII) (XXII)



(CLXXXVI) (CLXXXVII) (CLXXXVIII)

From the above study on the hydrogenolysis of steroidal cyclic acetals the following salient points of interest may be drawn:

(a) The reaction is steric - approach controlled or kinetically controlled (i.e. where the product is formed regardless of stability consideration).

(b) The reductive cleavage of dioxolane ring follows the accepted mechanism.

(c) 3α,5α-cyclopropane ring in 6-acetals provides a seat for rearrangement (via a homoallylic cation) and consequently isomeric hydroxyethers were also obtained, besides the expected ethers.

(d) 3α,5α-cyclopropane ring or a double bond at C_4-C_5 in 6-acetals led to the formation of hydrocarbons as products of elimination and/or substitution besides hydroxy ethers, and

(e) In all the cases studied only the corresponding β-hydroxyethers were obtained except in the case of 6-bromo-3,3-ethylenedioxycholest-5-ene (XXI) where a small amount of the α-epimer was also obtained along with the β-epimer which constituted the major product of the reaction. This difference in the behaviour of the bromoacetal (XXI) may be explained on the basis of steric hinderance offered by bromine atom at C6 to the incoming reducing species (AlH_2Cl) to the reaction site. The preferred course of the attack by AlH_2Cl on the acetal ring

is from the less hindered rear side. The presence of bromine at C6 may offer steric hinderance to the incoming AlH_2Cl from the rear side and therefore a small amount of reactive species may also attack from the front side to give the α-hydroxyether (XXII)[60].

With this background, the present study was undertaken in order:

(a) to extend the $LiAlH_4$-$AlCl_3$ reduction to other unexplored yet easily accessible steroidal cyclic acetals, specially those derived from steroidal diones,

(b) to study the effect of C4-C5-double bond on the hydrogenolysis of steroidal bisacetals of 3,6-diones,

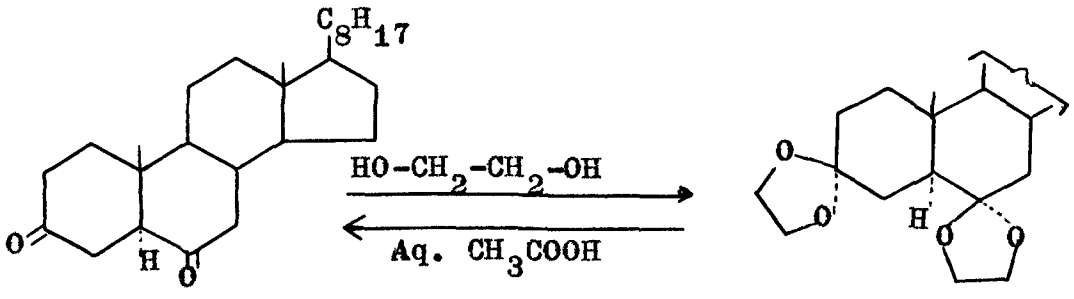
(c) to evaluate the synthetic utility of the reactions in steroidal systems and

(d) to check the validity of the accepted mechanism of hydrogenolysis of steroidal cyclic acetals in general.

For the present study 5α-cholestane-3,6-dione (CLXXXIX), cholest-4-ene-3,6-dione (XLVII) and 5-hydroxy-5α-cholestane-3, 6-dione (CXC) were selected.

Preparation of Steroidal cyclic acetals.
3,3,6,6-Bisethylenedioxy-5α-cholestane (CXCI).

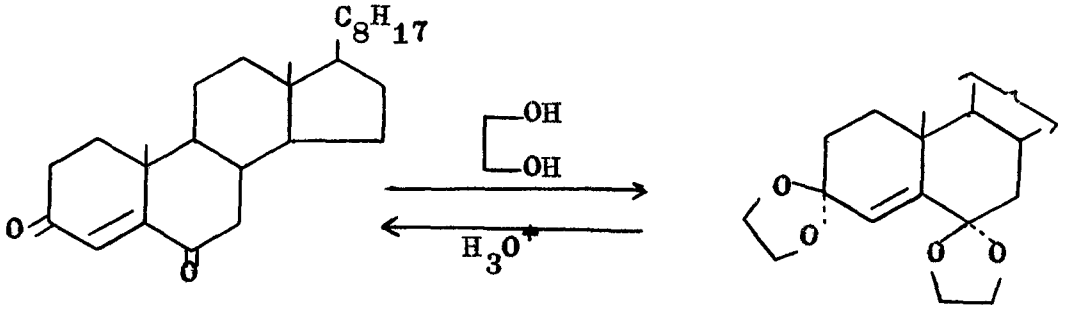
3,3,6,6-Bisethylenedioxy-5α-cholestane (CXCI) was prepared by the reaction of 5α-cholestane-3,6-dione (CLXXXIX) with ethylene glycol in the presence of catalytic amount of p-toluenesulphonic acid monohydrate. (The dione (CLXXXIX), m.p. 166°C was prepared according to the method described in literature[73]). After usual work up of the reaction mixture, the bisacetal (CXCI) was purified by column chromatography and its homogeneity checked by t.l.c. The bisacetal (CXCI), m.p. 120°, analysed correctly for $C_{31}H_{52}O_4$ and its i.r. spectrum showed absorption peaks at 1145, 1039 and 1035 cm^{-1} (C-O-linkage of the acetal rings). The n.m.r. spectrum of the bisacetal (CXCI) gave signals at δ3.86 mc (8 protons, C3-O-CH_2-CH_2-O-; C6-O-CH_2-CH_2-O-), δ0.7, 0.83, 0.93 (methyl protons). Treatment of the bisacetal (CXCI) with aqueous acetic acid regenerated the parent dione (CLXXXIX) quantitatively.



(CLXXXIX) (CXCI)

3,3,6,6-Bisethylenedioxycholest-4-ene (CXCII).

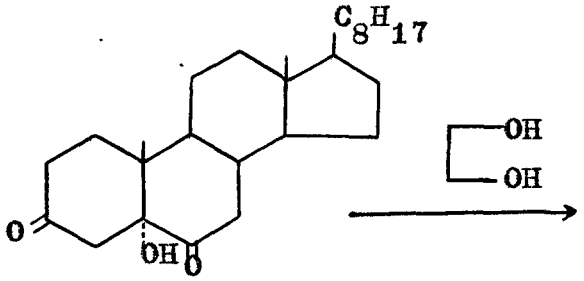
The enedione, cholest-4-ene-3,6-dione (XLVII) used in the present study was prepared according to literature procedure[137] (m.p. 122°, M^+ 398, $C_{27}H_{42}O_2$; $\nu_{max.}$ 1680s, 1615, 1595 cm^{-1}; $\lambda_{max.}$ 252 nm, (ϵ 10,300); δ 6.16s (C_4-H), 2.6 mc(C_2-H_2 and C_7-H_2). The enedione (XLVII) with ethylene glycol in the presence of p-toluenesulphonic acid monohydrate (as catalyst) afforded the bisacetal, 3,3,6,6-bisethylenedioxycholest-4-ene (CXCII) which was purified by column chromatography (t.l.c. homogeneous). The bisacetal (CXCII), m.p. 136°, analysed correctly for $C_{31}H_{50}O_4$ and its i.r. spectrum showed peaks at 1640 (C=C), 1170, 1134, 1073, and 1034 cm^{-1} (C-O- linkage of the acetal rings). The n.m.r. spectrum of (CXCII) gave signals at δ 5.85 (1 proton, C4-H, vinylic proton), 3.85 mc (8 protons, C3-O-CH_2-CH_2-O-; C6-O-CH_2-CH_2-O-), 1.2, 0.8, 0.7 (methyl protons). The bisacetal (CXCII) on treatment with aqueous acetic acid or dilute HCl regenerated the parent ketone (XLVII).



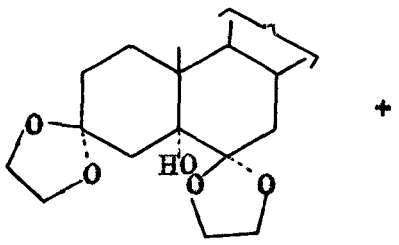
(XLVII) (CXCII)

5-Hydroxy-3,3,6,6-bisethylenedioxy-5α-cholestane (CXCIII).

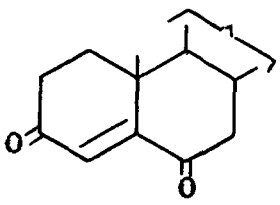
5-Hydroxy-5α-cholestane-3,6-dione (CXC), m.p. 255°, was prepared according to the method described by Fieser[138]. The formation of the bisacetal (CXCIII) from the hydroxydione (CXC) with ethyleneglycol and p-toluenesulphonic acid monohydrate (as catalyst) was rather slow and more complicated in comparison with the previous examples. After usual work up of the reaction mixture, it was found to be a mixture of atleast 3 components (t.l.c.) and column chromatography provided three distinct products, m.pts. 124°, 122° and 136°.



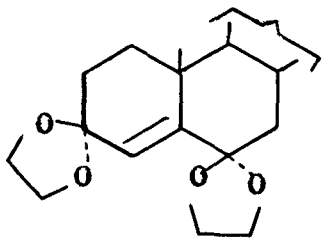
(CXC)



(CXCIII)



(XLVII)



(CXCII)

Characterization of the compound, m.p. 124° as 5-hydroxy-3,3, 6,6-bisethylenedioxy-5α-cholestane (CXCIII).

The compound, m.p. 124° analysed correctly for $C_{31}H_{52}O_5$ and its i.r. spectrum showed absorption peaks at 3550 (sharp, -OH), 1180, 1125, 1086 and 1052 cm^{-1} (C-O-). The n.m.r. spectrum gave signals at δ3.9 mc (8 protons, C3-O-CH_2-CH_2-O-; C6-O-CH_2-CH_2-O-), 1.06, 0.9, 0.8 and 0.7 (methyl protons).

Characterization of the compound, m.p. 136° as 3,3,6,6-bisethylenedioxycholest-4-ene (CXCII).

The compound, m.p. 136° analysed correctly for $C_{31}H_{50}O_4$. From its composition and m.p. it was obvious that the product at hand was the bisacetal (CXCII) which was previously prepared from the enedione (XLVII). The i.r. and n.m.r. spectra of this product were superimposable with those of the bisacetal (CXCII) obtained in the previous experiment. Further a mixed m.p. determination with (CXCII) showed no depression. It is reasonable to believe that the hydroxydione (CXC) suffered ready dehydration under reaction conditions to give the enedione (XLVII); the latter was subsequently converted into the bisacetal (CXCII).

Characterization of the compound m.p. 122° as cholest-4-ene-3,6-dione (XLVII).

The compound, m.p. 122° analysed correctly for $C_{27}H_{42}O_2$ and from m.p., mixed m.p., i.r. and n.m.r. spectra, this product

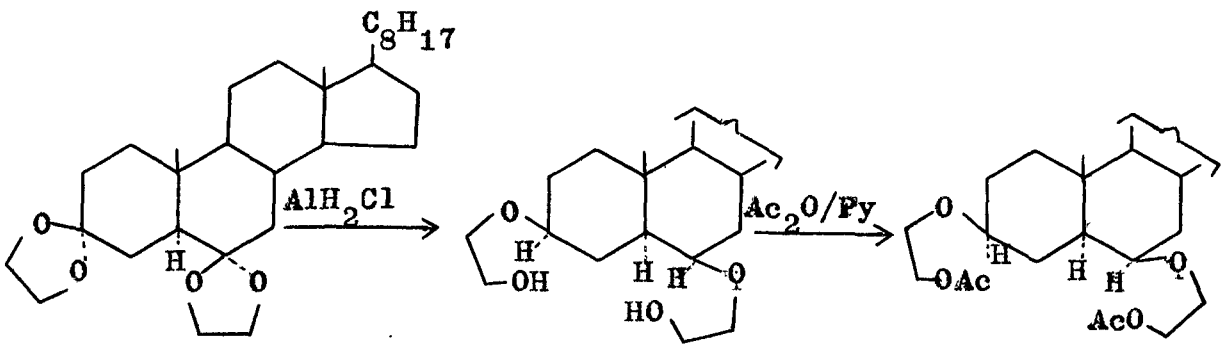
was found to be identical with cholest-4-ene-3,6-dione (XLVII)[73].

Hydrogenolysis of steroidal bisacetals.

Hydrogenolysis of the bisacetals in the present study was carried out according to published directions[61,62] using an equimolar mixture of lithium aluminium hydride and anhydrous aluminium chloride in dry diethyl ether. The products of hydrogenolysis were purified by column chromatography and crystallization, and their homogeneity was ascertained by thin layer chromatography. The identification of the products was made with the aid of elemental analysis, i.r. and n.m.r. spectra, and degradative studies.

$LiAlH_4$-$AlCl_3$ Reduction of 3,3,6,6-bisethylene⇒dioxy-5∝-cholestane (CXCI).

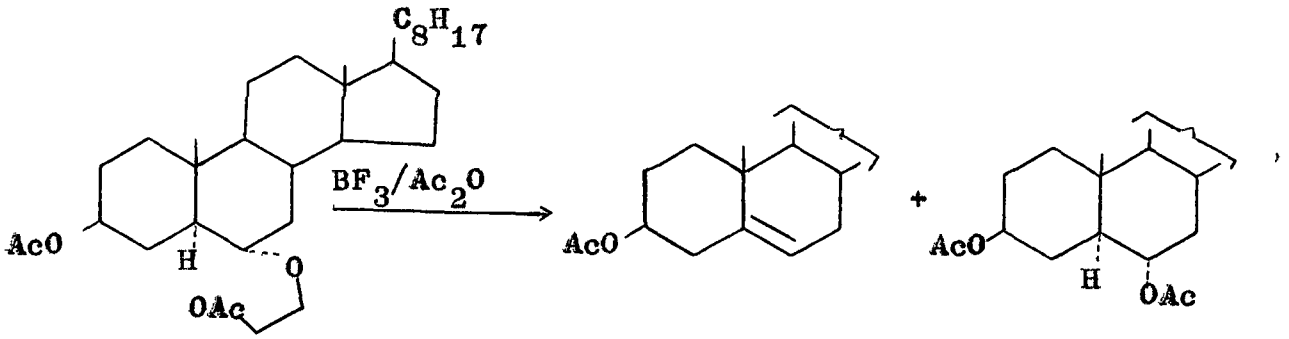
Hydrogenolysis of 3,3,6,6-bisethylenedioxy-5∝-cholestane (CXCI) with $LiAlH_4$-$AlCl_3$ (molar ratio 1:1) gave a single product, m.p. 174°, which was identified as 3β,6β-(2',2"-bishydroxyethoxy)-5∝-cholestane (CXCIV).



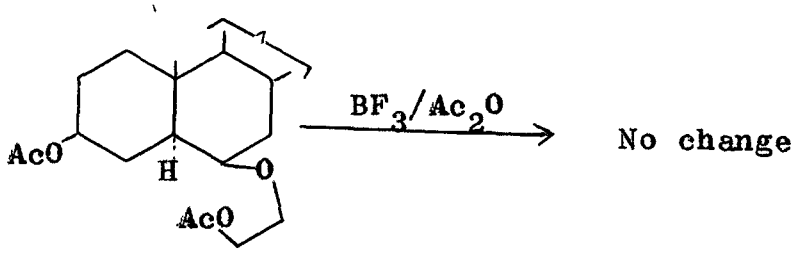
(CXCI) (CXCIV) (CXCV)

The bishydroxy ether (CXCIV), m.p. 174°, analysed correctly for $C_{31}H_{56}O_4$ and its i.r. spectrum showed peaks at 3450 (br,-OH), 1100, 1040 and 1020 cm^{-1} (C-O-). Its n.m.r. spectrum gave a multiplet centred at δ 3.66 which integrated for 8 protons ascribable to C_3-O-C$\underline{H}_2$-C$\underline{H}_2$-O- and C_6-O-C$\underline{H}_2$-C$\underline{H}_2$-O- and another multiplet centred at δ 3.3 integrating for 2 protons which were assigned to C_3-$\underline{H}$ and C_6-$\underline{H}$. Since the C3 and C6 protons are merged together, it was rather difficult to assign the configurations of the ether moieties at C3 and C6 by measuring the half-band widths of C3-$\underline{H}$ and C6-$\underline{H}$ peaks. Configurational assignments of ether moieties at C3- as β (equatorial) and C6- (β-axial) at this stage have been made tentatively by analogy[60-63]. Treatment of the hydroxyether (CXCIV) with acetic anhydride and pyridine gave 3β,6β(2',2"-bisacetoxyethoxy)-5α-cholestane (CXCV). The diacetate (CXCV), m.p. 143°, analysed correctly for $C_{35}H_{60}O_6$ and its i.r. spectrum gave peaks at 1735, 1240 (CH_3COO), 1100, 1040, and 1020 cm^{-1}(C-O-). The n.m.r. spectrum of the diacetate (CXCV) gave signals at δ 4.16 (dist. t, 4 protons, C3-O-CH_2-C$\underline{H}_2$-OAc; C6-O-CH_2-C$\underline{H}_2$-OAc), 3.6 (t, 4 protons, C3-O-C$\underline{H}_2$-CH_2-OAc; C6-O-C$\underline{H}_2$-CH_2-OAc), 3.28 (mc, 2 protons C3-$\underline{H}$ and C6-$\underline{H}$), and 2.1 (s; 6 protons C3-O-CH_2-CH_2-O-$\overset{O}{\overset{\|}{C}}$-C$\underline{H}_3$ C6-O-CH_2-CH_2-O-$\overset{O}{\overset{\|}{C}}$-C$\underline{H}_3$). Again, configurational assignment of ether moieties at C3 and C6 could not be made because of the merger of the C3-H and C6-H signals.

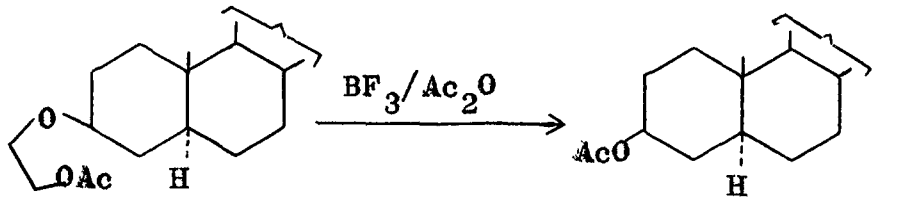
However, the stereochemistry of C3 and C6-ether moieties in the diacetate (CXCV) was determined by following an indirect route. Advantage was taken of the fact that whereas 6α-acetoxy-ether (equatorial) such as (CXCVI) was cleaved or degraded by BF_3-etherate-acetic anhydride[64], the 6β-epimer (axial) (CLXXVII) remained indifferent towards this reagent[62]. On the other hand the 3β-acetoxyether (equatorial) (CXCIX) with BF_3-etherate-acetic anhydride gave 3β-acetoxy-5α-cholestane (CC) as the major product[13



(CXCVI) (CXCVII) (CXCVIII)

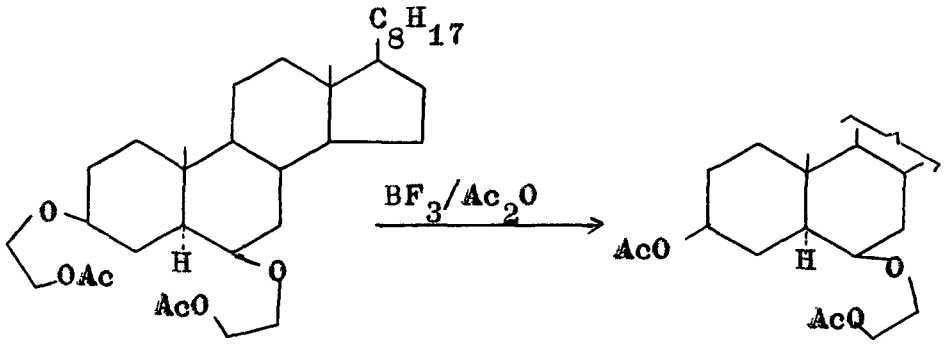


(CLXXVII)



(CXCIX) (CC)

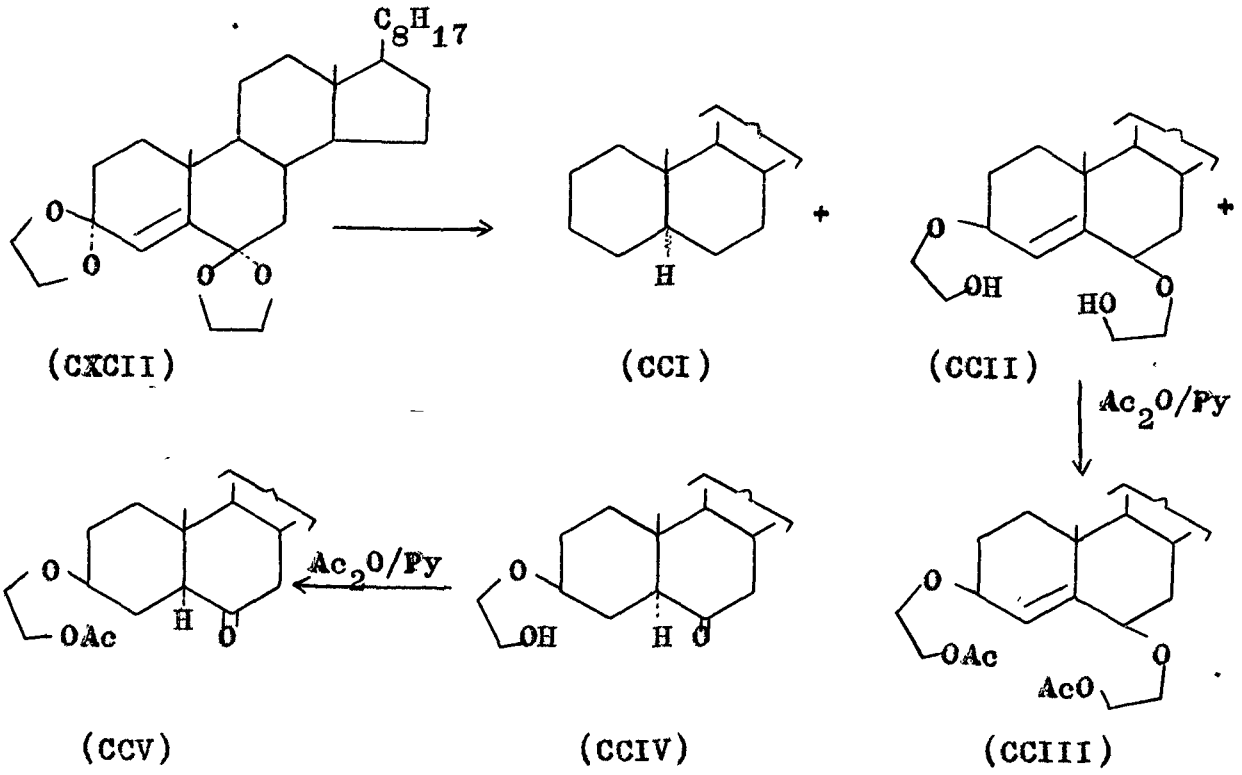
3β,6β-(2',2"-Bisacetoxyethoxy)-5α-cholestane (CXCV) when subjected to BF_3-etherate-acetic anhydride degradation gave 6β-(2'-hydroxyethoxy)-5α-cholestan-3β-ol 2',3-diacetate (CLXXVII), as the major product. The diacetate (CLXXVII), m.p. 76-77° was found to be identical with an authentic sample of (CLXXVII, m.p., mixed m.p., i.r., n.m.r. and t.l.c. identical)[62,64]. This degradative study is suggestive of the fact that the ether moiety at C3 is equatorial (β) whereas at C6 it is axial (β).



(CXCV) (CLXXVII)

<u>$LiAlH_4$-$AlCl_3$ Reduction of 3,3,6,6-bisethylenedioxycholest-4-ene (CXCII).</u>

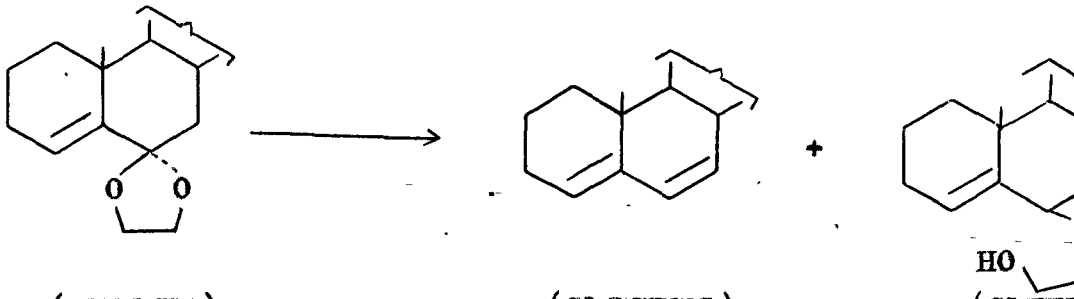
The reductive cleavage of the heterocyclic rings in 3,3,6,6-bisethylenedioxycholest-4-ene (CXCII) using the standard procedure gave a mixture of atleast 3 components as revealed by t.l.c. Column chromatography of the crude reaction product gave three compounds, m.pts. 62°, 126° and 109° and were characterized by usual methods.



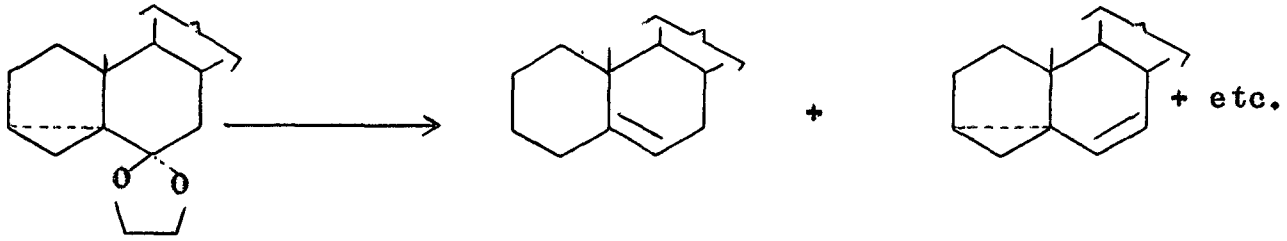
The 'Compound' m.p. 62°.

This 'Compound' (CCI) analysed correctly for $C_{27}H_{48}$ (M^+ 372; the fragmentation pattern was similar to cholestanes)[140]. It did not give positive test with tetranitromethane and its i.r. spectrum was devoid of any significant peaks. Its n.m.r. spectrum was featureless in the region δ1.8-10. Since its m.p. did not correspond either to 5α-cholestane (m.p. 80°) or 5β-cholestane (m.p. 70°), it was obviously thought to be a mixture of the two. The formation of saturated hydrocarbon is interesting in the sense that whereas the other unsaturated acetal (CLXXXVI) or

the acetal containing 3α,5α-cyclopropane moiety gave products of eliminations as well under reductive conditions, this one (CXCII) gave saturated hydrocarbon/s as one of the products.



(CLXXXVI) (CLXXXVII) (CLXXXVIII)



(XXIV) (XXVI) (XXVII)

Characterization of the compound m.p. 126° as 3β,6β(2',2"-bishydroxyethoxy)cholest-4-ene (CCII).

The compound, m.p. 126° analysed correctly for $C_{31}H_{54}O_4$ and gave positive test with tetranitromethane. Its i.r. spectrum gave peaks at 3450br(OH), 1650(C=C), 1098, 1067, and 1040 cm^{-1} (C-O-). Its n.m.r. spectrum gave a doublet like signal at δ 5.9 integrating for 1 proton ascribable to C4-H (vinylic proton) and a multiplet centred at δ 3.73 integrating for 10 protons (C3-O-C<u>H</u>$_2$-C<u>H</u>$_2$-O; C6-O-C<u>H</u>$_2$-C<u>H</u>$_2$-O-; C3-<u>H</u> and C6-<u>H</u>). The signals

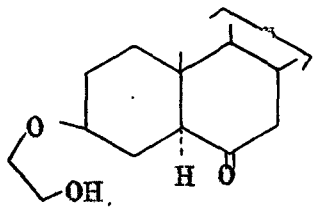
for C3-H and C6-H shifted downfield as compared with the same protons in the saturated homologue (CXCIV) where C3-H and C6-H are bunched together at δ 3.3. This is understandable since in the case of the unsaturated ether (CCII) both C3-H and C6-H are at allylic positions to C4-C5 double bond. Since the signals for C3-H and C6-H merged with other signals, it was not possible to ascertain the configurations of C3-and C6-ether moieties.

Treatment of the bishydroxyether (CCII) with acetic anhydride gave the corresponding diacetate (CCIII) as a non-crystallizable oil (purified by column chromatography, homogeneous by t.l.c.). The diacetate (CCIII) analysed correctly for $C_{35}H_{58}O_6$ and its i.r. spectrum showed peaks at 1736, 1235 ($CH_3 - \overset{O}{\overset{\|}{C}} - O-$), 1650 (C=C), 1100, 1040, and 1025 cm^{-1} (C-O-). The n.m.r. spectrum of the diacetate (CCIII) gave signals at δ5.88 (doublet like, 1 proton, C4-H), 4.1 mc (triplet like, 4 protons, $C3-O-CH_2-CH_2-OAc$; $C6-O-CH_2-CH_2-OAc$), 3.8 mc (2 protons, C3-H and C6-H), 3.55 (triplet like, 4 protons, $C3-O-CH_2-CH_2-OAc$; $C6-O-CH_2-CH_2-OAc$); 2.01s (3 protons) and 2.07s (3 protons) ($C3-O-CH_2-CH_2-O-\overset{O}{\overset{\|}{C}}-CH_3$ and $C6-O-CH_2-CH_2-O-\overset{O}{\overset{\|}{C}}-CH_3$).

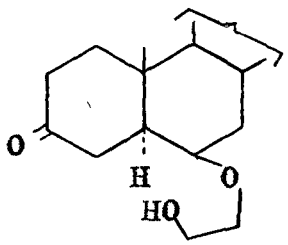
Again the signals for C3-H and C6-H are merged together and therefore configurational assignments of C3- and C6-ether moieties could not be made by measuring half-band widths of C3-H and C6-H signals. However, by analogy, the configurations of the ether moieties have been assigned as C3β-(equatorial) and C6β-(axial).

Characterization of the compound, m.p. 109° as 3β-(2'-hydroxyethoxy)-5α-cholestan-6-one (CCIV).

The compound, m.p. 109° analysed correctly for $C_{29}H_{50}O_3$ and its i.r. spectrum showed peaks at 3550(OH), 1710 (C=O), 1098, 1062 and 1040 cm^{-1} (C-O-). The presence of a saturated carbonyl group in the compound suggested that the reduction was complicated in the sense that only one of the acetal ring systems suffered hydrogenolysis together with the reduction of C4-C5 double bond. The remaining acetal ring on subsequent work up with dilute H_2SO_4 regenerated that ketone moiety. This leads to two possibilities, (CCIV) and (CCVI).



or



(CCIV) (CCVI)

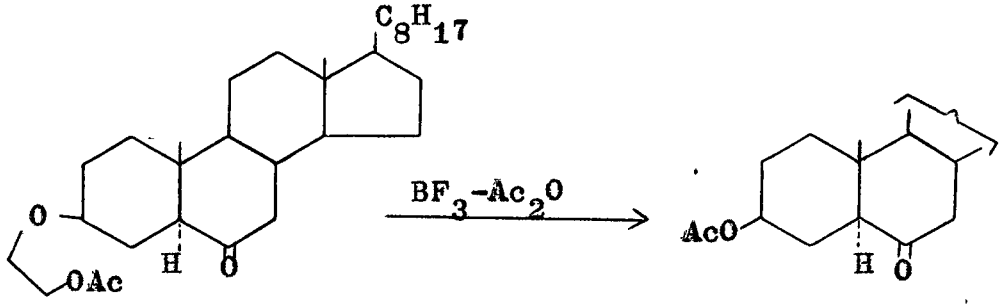
That the product was not a mixture was ascertained by t.l.c. in different solvent systems. The n.m.r. spectrum of the compound, m.p. 109°C, gave signals at δ 3.7 mc (4 protons) ascribable to C3-O-$\underline{CH}_2$-$\underline{CH}_2$- or C6-O-$\underline{CH}_2$-$\underline{CH}_2$-O-; 3.1br (1 proton) C3-$\underline{H}$ or C6-$\underline{H}$ and 2.25 mc (2 protons; -$\overset{\overset{O}{\|}}{C}$-$CH_2$-). There was no indication of a vinylic proton. The magnitude of splitting of the peak centred

at δ3.1 with half band width of 16 Hz suggested that this proton is axial and that it is interacting with at least 4 protons (2 axial and 2 equatorial protons). Further the signal at δ 2.2 integrating for 2 protons suggested the presence of one methylene group α- to a carbonyl group. These observations strongly suggested that the comound, m.p. 109° has the structure (CCIV). On steric ground also, it is to be expected that the acetal ring system concerned with C3 will be preferentially hydrogenolysed in comparison to the one at C6.

The keto-hydroxyether (CCIV) was readily converted into its acetate (CCV), m.p. 105°, on treatment with acetic anhydride and pyridine. The keto-acetate (CCV), analysed correctly for $C_{31}H_{52}O_4$ and its i.r. spectrum gave peaks at 1736, 1235 ($CH_3-\overset{O}{\overset{\|}{C}}-O-$) and 1710 (C=O), The n.m.r. spectrum gave signals at δ4.1t (2 protons, C3-O-CH_2-$\underline{CH}_2$-OAc), 3.70t (2 protons, C3-O-$\underline{CH}_2$-CH_2-OAc), 3.1br (1 proton, $W\frac{1}{2}$ 16 Hz, C3-H,αaxial), 2.3 mc (2 protons, $\underline{CH}_2-\overset{O}{\overset{\|}{C}}-$), and 2.0s (3 protons, $-O-\overset{O}{\overset{\|}{C}}-\underline{CH}_3$).

From the n.m.r. spectra of the ketoether (CCIV) and keto-acetate (CCV), it is obvious that the configuration of the ether moiety at C3 is equatorial (β-oriented). This conclusion was further supported by the degradative studies. The keto-acetate (CCV) on treatment with BF_3-etherate-acetic anhydride provided 3β-acetoxy-5α-cholestan-6-one (CXV) as the major product. This

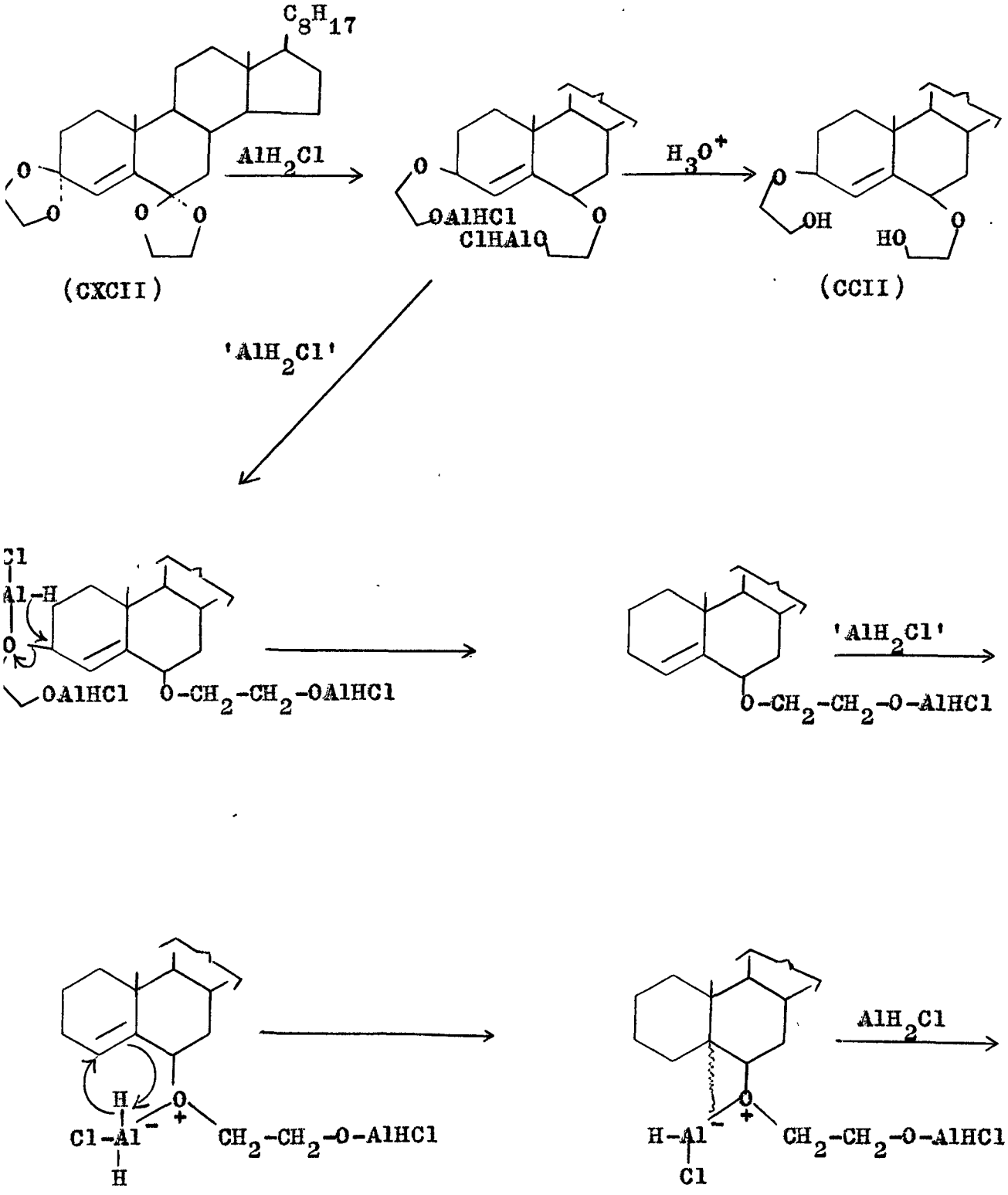
not only helped in the assignment of the configuration of the ether moiety but also supported the structure of the keto-acetate as (CCV).

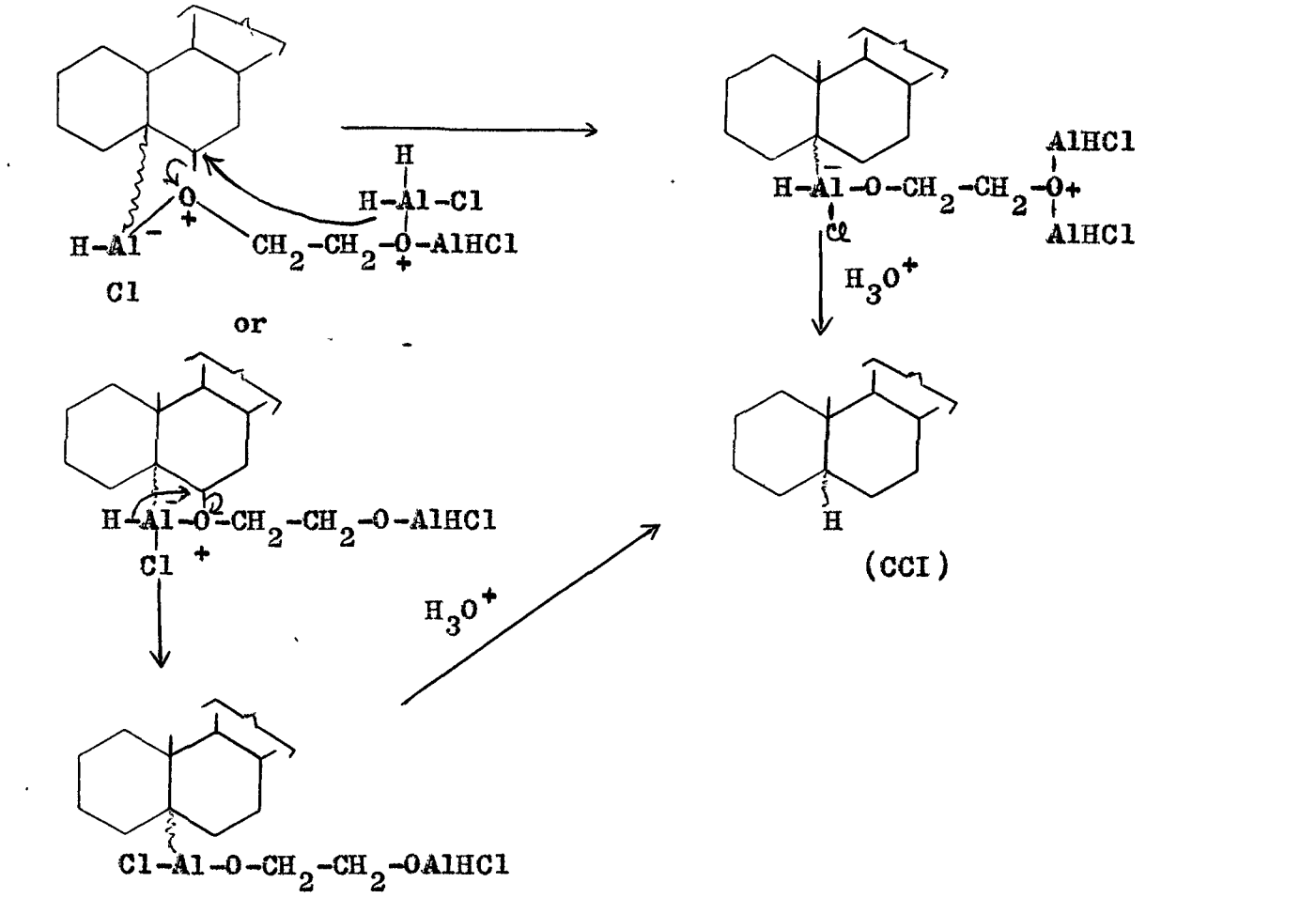


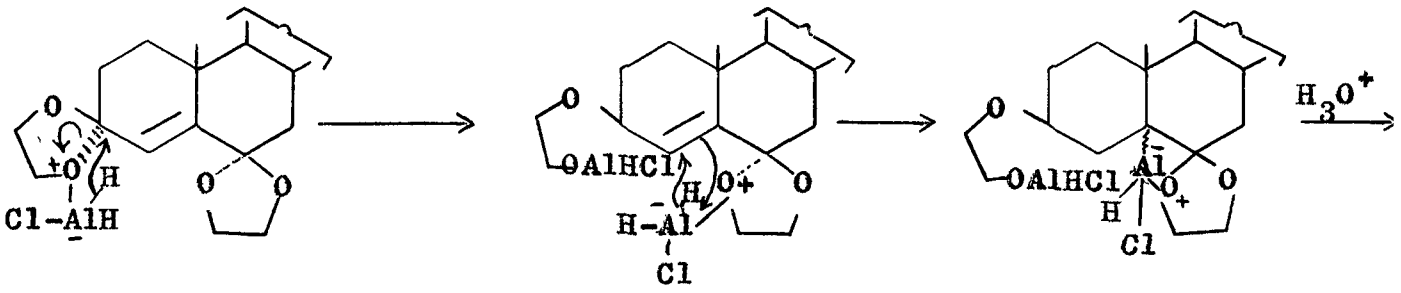
(CCV) (CXV)

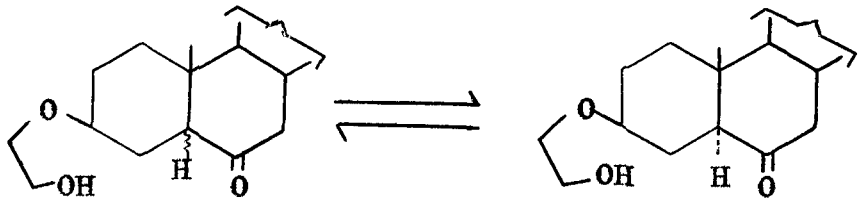
The formation of the saturated hydrocarbon/s (CCI) and the keto-ether (CCIV) from the hydrogenolysis of the bisacetal (CXCII) is intriguing. A tentative mechanism for the formation of (CCI) and (CCIV) is given below. Apparently, one or more pathways have to be considered to account for 3 products of hydrogenolysis. According to the accepted mechanism of hydrogenolysis of steroidal cyclic acetals by $LiAlH_4$-$AlCl_3$, the bisacetal (CXCII) is attacked by reducing agent (AlH_2Cl) at the rear oxygen atoms of the acetal moieties at C3 and C6 leading to the normal product, i.e. the bis-hydroxyether (CCII). This then suffers further changes to give the hydrocarbon product (CCI).

On the other hand, the bisacetal (CXCII) may be attacked preferentially at C3-acetal moiety and this course then can lead to the C3-acetal ring cleavage and reduction of C4-C5 double bond.


C8H17
AlH2Cl
H3O+
OAlHCl
ClHAlO
OH
HO
(CXCII)
(CCII)
'AlH2Cl'
Cl
Al-H
O
OAlHCl
O-CH2-CH2-OAlHCl
'AlH2Cl'
O-CH2-CH2-O-AlHCl
H
Cl-Al
H
CH2-CH2-O-AlHCl
AlH2Cl
H-Al
Cl
CH2-CH2-O-AlHCl


H-Al-Cl
H-Al
Cl
CH2-CH2-O-AlHCl
or
H-Al-O-CH2-CH2-O-AlHCl
Cl
AlHCl
H-Al-O-CH2-CH2-O+
AlHCl
H3O+
H
(CCI)
H3O+
Cl-Al-O-CH2-CH2-OAlHCl

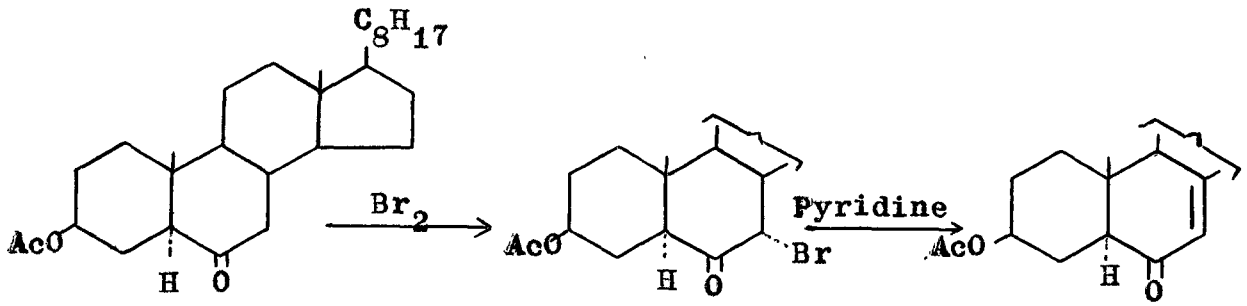

Cl-AlH
OAlHCl
H-Al
Cl
H3O+
OAlHCl
H
Cl


OH
H
O
OH
H
O

(CCIV)

α-Bromination of 3β-acetoxy-5α-cholestan-6-one (CXV)

In order to prepare 3β-acetoxy-5α-cholest-7-en-6-one (CCVIII) according to the following scheme, the preparation of 3β-acetoxy-7α-bromo-5α-cholestan-6-one (CCVII) was undertaken according to the method described by Heilbron and coworkers since they studied the mono- and dibromination of the title compound (CXV)[73,76].

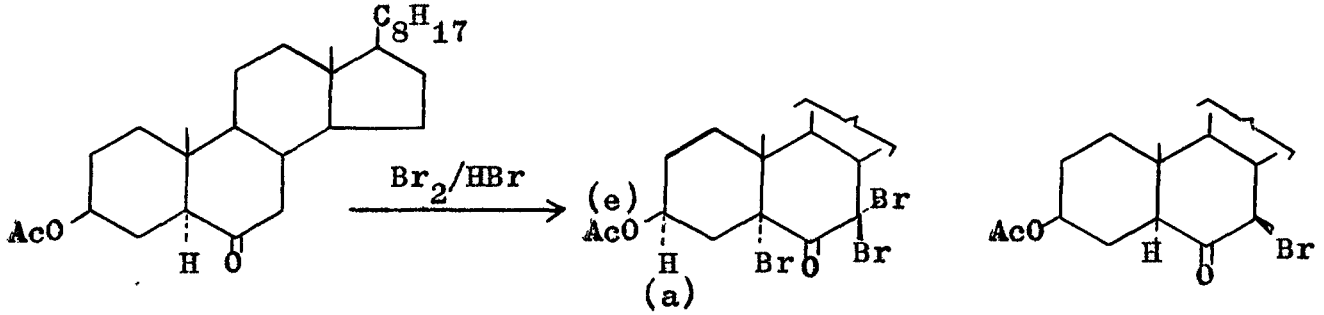


(CXV) (CCVII) (CCVIII)

When 3β-acetoxy-5α-cholestan-6-one (CXV) was treated with Br_2/HBr in ether-acetic acid under reflux for 2 hours and the reaction mixture, after removal of the ether solvent, set aside for 24 hours, it invariably afforded a product, m.p. 186°, after column chromatography and crystallization. In one or two experiments, under similar conditions, a product, m.p. 140°, was obtained. None of these products was found to be the desired 7α-bromoketone (CCVII).

Characterization of the compound, m.p. 186° as 3β-acetoxy-5,7,7-tribromo-5α-cholestan-6-one (CCIX).

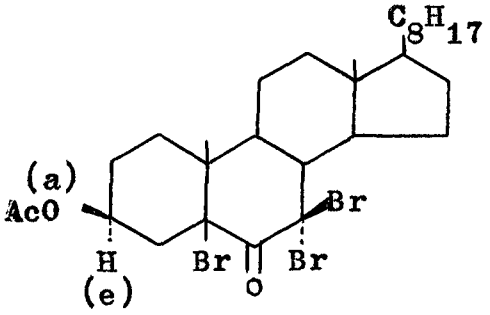
The compound, m.p. 186° (positive Beilstein test) analysed correctly for $C_{29}H_{45}O_3Br_3$. From the composition, it is evident that 3 bromine atoms were introduced at α-positions to the C6-carbonyl group. The i.r. spectrum of the compound (CCIX) gave peaks at 1739, 1221 (CH_3-COO-), 1720 (C=O) and 750 cm^{-1} (C-Br)[143]. Its n.m.r. spectrum (100 MHz) gave signals at δ 5.4m (1 proton C3-H, axial, α-oriented, 7-peaks J = 10 and 5 Hz)[141], 2.05s (3 protons, CH_3-COO), 1.05 (C10-Me), 0.78 (C13-Me), 0.98, 0.92 and 0.85 (other methyl protons); no other signal was observed in the region δ2.5-10.



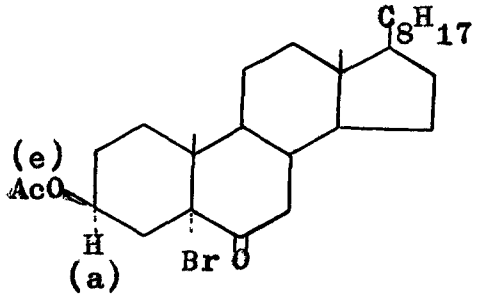
(CXV) (CCIX) (CCX)

The signal for C3-H appeared at relatively low field i.e. at δ5.4. Generally the C3-H (α, axial) in compounds of the type (CXV) gives signal at about δ4.7-5. This downfield shift of C-3H signal in the tribromide (CCXI) led to the suspicion that Br

at C5 is β (equatorial, A/B ring junction cis), thus causing C3α-H to be equatorial, which would appear in the downfield region (structure CCXI). In order to remove this doubt, the n.m.r. spectrum of the known 5α-bromocompound, 3β-acetoxy-5-bromo-5α-cholestan-6-one (CCXII) was determined.



(CCXI)



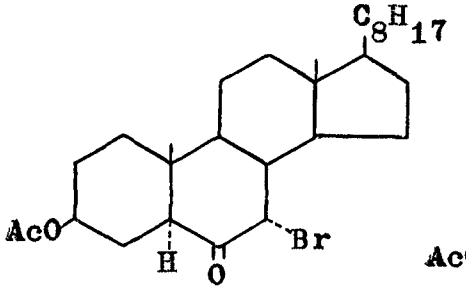
(CCXII)

The n.m.r. spectrum (100 MHz) of the 5α-bromoketone (CCXII) gave signals at δ5.35m (1 proton, C3-$\underline{H}$, axial, α-, 7-peaks, J=10 and 5 Hz), 2.3d like (2 protons, C7-$\underline{H}_2$-$\overset{O}{\overset{\|}{C}}$-) 2.02s (3 protons, $C\underline{H}_3$-COO-), 1.0, (C10-Me), 0.7 (C13-Me), 0.92 and 0.83 (other methyl protons). The striking similarity between the signals of C3-H protons in the tribromide (CCIX) and 5α-bromoketone (CCXII) in terms of splitting magnitude and shape leaves no doubt that in the tribromide (CCIX), the C5-Br is axial. The downfield shift of C3-H may be attributed to the presence of C5α-Br. It is pertinent to mention that in steroidal C3-acetate (β-equatorial) the signal for C3-H (α-axial) appears as septet

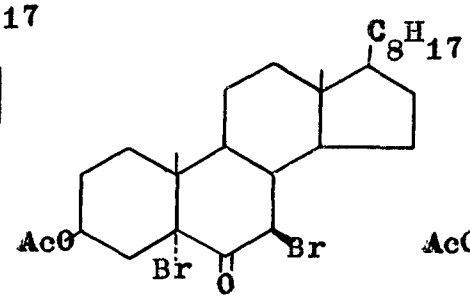
with J=10 and 5 Hz, in 100 MHz spectrum, though at a higher field (say in the region δ 4.7-5)[141].

Characterization of the compound, m.p. 140° as 3β-acetoxy-5,7β-dibromo-5α-cholestan-6-one (XLV).

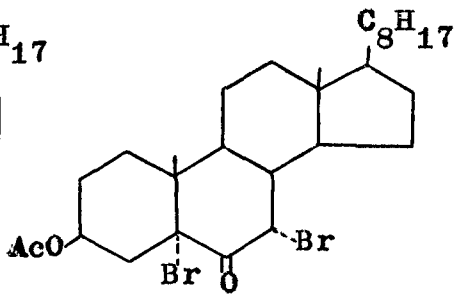
The compound, m.p. 140°, analysed correctly for $C_{29}H_{46}O_3Br_2$ (positive Beilstein test) and its i.r. spectrum showed peaks at 1732, 1250 (CH_3COO-), 1710 (C=O), and 750 cm^{-1} (C-Br). Heilbron and coworkers[73], have reported the m.p. 129° for the dibromide (XLV) and 145° for 3β-acetoxy-7α-bromo-5α-cholestan-6-one (CCVII). The closeness in m.p.ts. of our compound (140°) and that of 7α-bromo compound (CCVII) indicated the possibility that the compound m.p. 140° could be 7α-bromo compound. However, elemental analysis eliminated this possibility. Further, the m.p. of 3β-acetoxy-5, 7α-dibromo-5α-cholestan-6-one (XLIV) is reported to be 152°.



(CCVII)
m.p. 145°



(XLV)

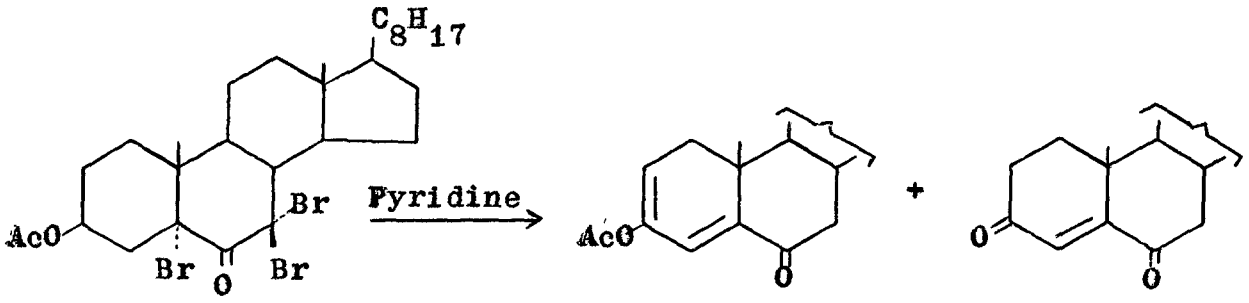


(XLIV)
m.p. 152°

The n.m.r. spectrum (100 MHz) of the compound, m.p. 140°, was very decisive in arriving at a definite conclusion. It gave signals at δ5.37d (J=9.5 Hz, 1 proton, C7-H, axial, α-oriented), 5.25br,m (1 proton, C3-H, axial, α-oriented), 2.04s (3 protons, CH_3-COO-), 0.98 (C10-Me), 0.70 (C13-Me), 0.95, 0.9 and 0.83 (other methyl signals). The appearance of a doublet (J=9.5 Hz) at δ5.37 and a broad multiplet centred at δ5.25 leaves no doubt as to the correctness of the structure (XLV) assigned to the compound, m.p. 140°. In the absence of a C5α-bromine the C3 proton was likely to give signal at about δ4.7. Although the signals at δ5.37 and 5.25 were overlapping in part, nevertheless they were clearly discernible. The structure of the dibromide (XLV) was further supported by dehydrobromination (refluxing pyridine) when it gave the known compound 3-acetoxycholesta-2, 4-dien-6-one (XLVI), reported earlier[78].

Dehydrobromination of 3β-acetoxy-5,7,7-tribromo-5α-cholestan-6-one (CCIX).

The tribromide (CCIX), m.p. 186°, was subjected to dehydrobromination with refluxing pyridine and after usual work up of the reaction mixture it gave two compounds as revealed by t.l.c. Column chromatography of the crude reaction product afforded two well defined crystalline products, m.p. 139° and 123°, respectively.



(CCIX) (XLVI) (XLVII)

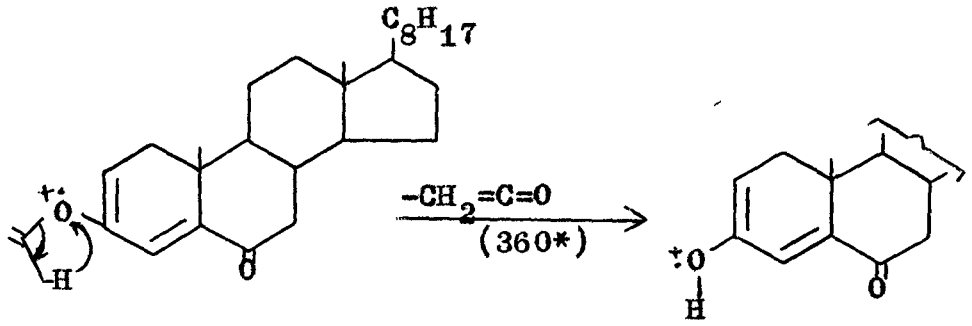
Characterization of the compound, m.p. 139° as 3-acetoxycholesta-2,4-dien-6-one (XLVI).

The compound, m.p. 139° (negative Beilstein test) analysed correctly for $C_{29}H_{44}O_3$ and its i.r. spectrum showed peaks at 1755 ($CH_3-\overset{O}{\overset{\|}{C}}-O-C=C$, enol acetate), 1675 (C=C-C=O), 1645 (-O-C=C), 1570 (C=C), and 1250 cm^{-1} (acetate). Its u.v. spectrum showed absorption maxima at 317 nm (reported[73,76] λmax. 317 nm). The n.m.r. spectrum displayed signals at δ6.57 (d, J=1.5 Hz, 1 proton C4-H; long range coupling with C2-H, $\wedge$ pattern), 5.67t (each splits into doublet, 1 proton, J=1.5 Hz, C2-H), 2.4d like (2 protons, CO-CH_2-C8-H), 2.05s (3 protons, CH_3-COO), 1.1 (C10-Me), 0.7 (C13-Me), 0.92, 0.90, 0.83 (other methyl signals).

The mass spectrum of the dienone acetate (XLVI)(Fig. 1) is very revealing and gave molecular ion peak at m/e 440 ($C_{29}H_{44}O_3$), with other significant peaks at m/e 425 (M-CH_3), m/e 412 (M-CO), m/e 398 (base peak; M-CH_2=C=O), m/e 383 (m/e 398-CH_3) and lower

20
40
60
80
100
40
80
120
160
200
240
280
320
360
400
440
460
41
43
109
120
135
227
247
382
383(398-CH3)
399
398 (M-CH2=C=O)
412(M-CO)
425(M-CH3)
440
AcO
O
C29H44O3
(M+ 440)
C8H17

mass peaks. The fragment ion m/e 398 (base peak) showed that the molecular ion loses a molecule of ketene (CH_2=C=O) and this assumption is well supported by a metastable peak at 360. The loss of a ketene molecule supports the presence of an enol acetate function; the loss of ketene is of common occurrence in enol acetates.

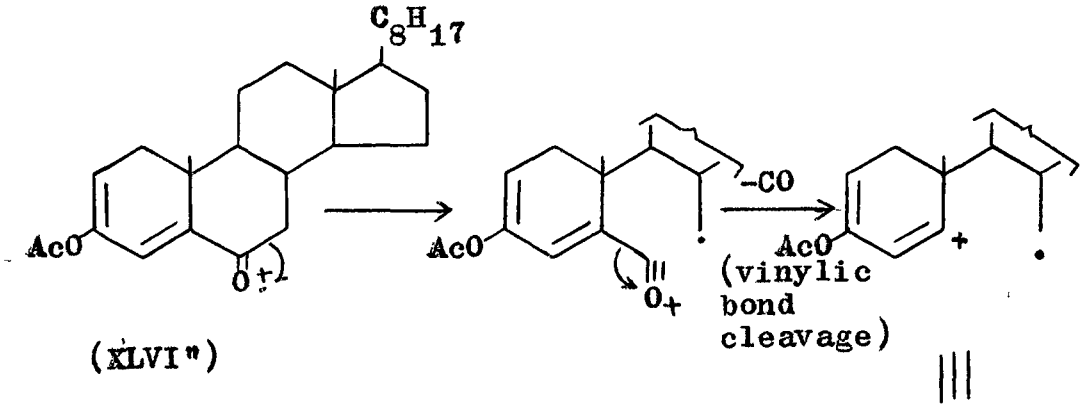


(XLVI) m/e 398

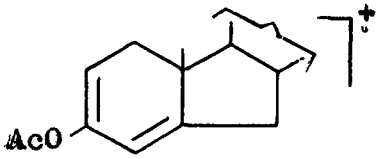
As anticipated the molecular ion did not show the loss of acetic acid since this would have involved two vinylic bonds cleavage, which is not considered to be a favourable process. (Loss of acetic acid from acetates occurs by 1,2-elimination).

The fragment ion peak at m/e 383 (m/e 398-CH_3) is also very pronounced and arises by the loss of a methyl group from the fragment ion m/e 398. This is supported by a metastable peak at 368.56. The M-CO peak at m/e 412 is very weak as the loss of CO from the molecular ion will involve the cleavage of

a vinylic bond at one stage or the other.

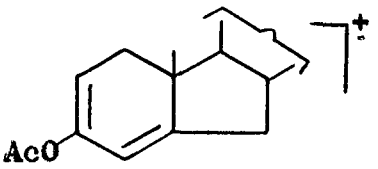


(XLVI")

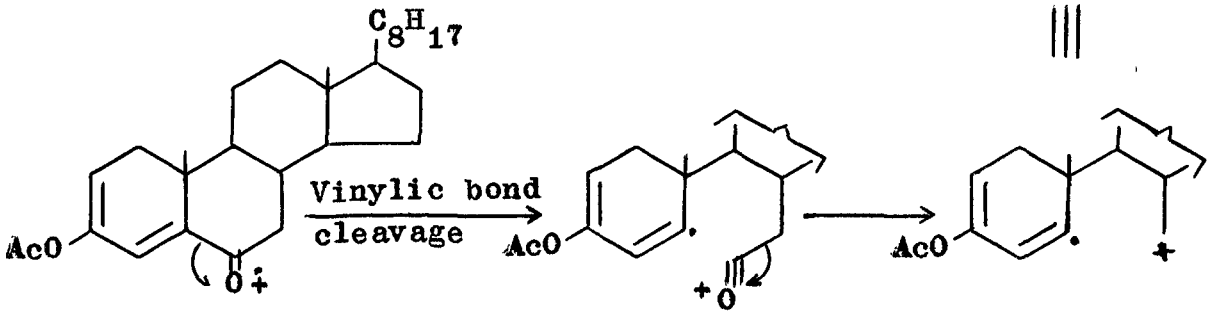


m/e 412

Or

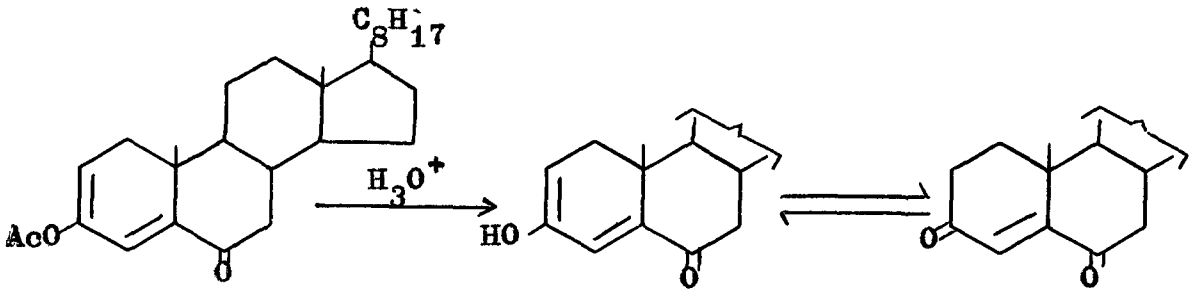


m/e 412



(XLVI")

Mild hydrolysis of 3-acetoxycholesta-2,4-dien-6-one (XLVI) gave the known compound, cholest-4-ene-3,6-dione (XLVII)[138].



(XLVI) (XLVII)

From the foregoing arguments it is evident that the compound m.p. 139° is 3-acetoxycholesta-2,4-dien-6-one (XLVI).

Characterization of the compound, m.p. 123° as cholest-4-ene-3,6-dione (XLVII).

The compound, m.p. 123°, (negative Beilstein test) analysed correctly for $C_{27}H_{42}O_2$ and its i.r. spectrum showed absorption bands at 1680 (C=C-C=O), 1615 and 1595 cm^{-1} (C=C-C=O). The presence of enedione moiety was further revealed by its u.v. spectrum (λmax. 252 nm, ϵ 11,000; reported λmax. 253 nm, ϵ 11,200)[78]. Its n.m.r. spectrum exhibited signals at δ 6.16s (1 proton, C4-H), 2.0-2.4m (4H, C2-H_2 and C7-H_2), 1.1 (C10-Me), 0.70 (C13-Me), 0.92, 0.90, and 0.83 (other methyl signals). The mass spectrum of (XLVII)(Fig. 2) gave molecular ion peak at m/e 398 ($C_{27}H_{42}O_2$), followed by significant peaks at m/e 383($M-CH_3$),

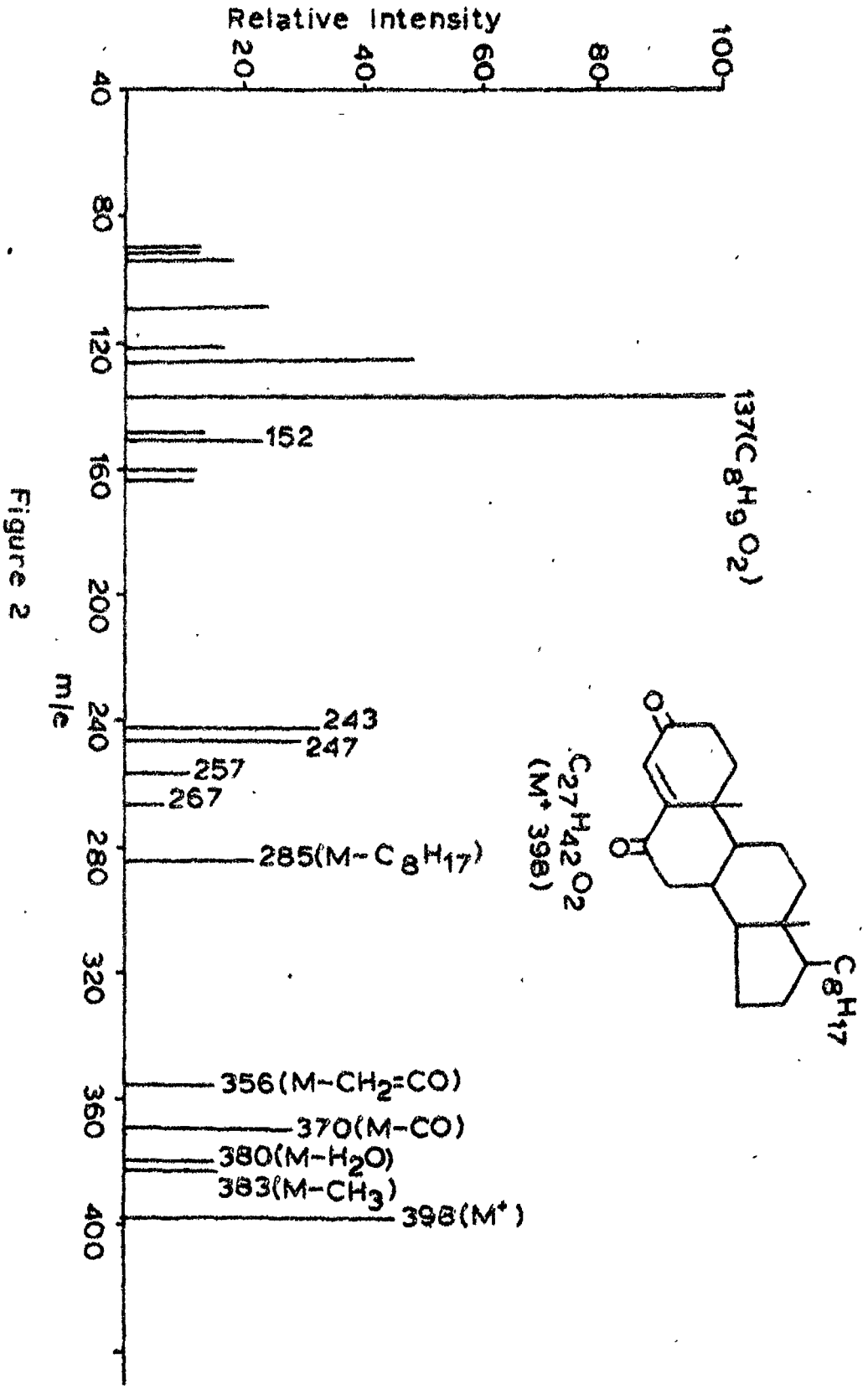
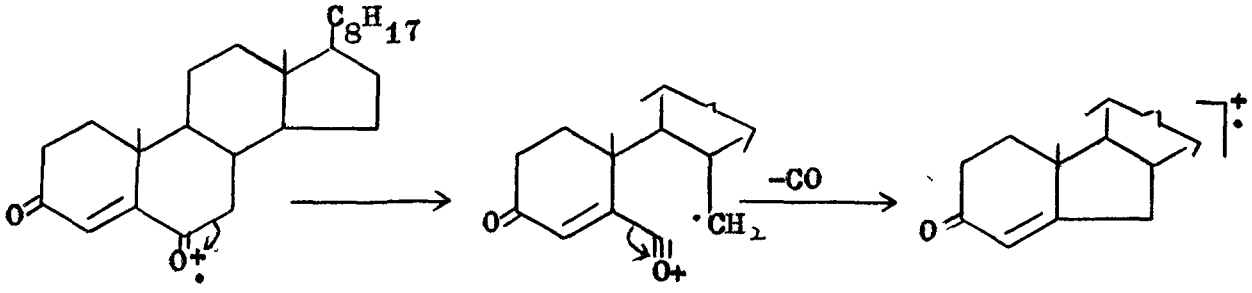

Relative Intensity
20
40
60
80
100
40
80
120
160
200
240
280
320
360
400
m/e
137($C_8H_9O_2$)
152
243
247
257
267
285(M-C_8H_{17})
356(M-CH_2=CO)
370(M-CO)
380(M-H_2O)
383(M-CH_3)
398(M^+)
$C_{27}H_{42}O_2$
(M^+ 398)
O
O
C_8H_{17}

Figure 2

m/e 380 ($M-H_2O$), m/e 370 (M-CO), m/e 356 ($M-CH_2=C=O$), m/e 285 ($M-C_8H_{17}$), m/e 267, m/e 257, m/e 247, m/e 244, m/e 243, m/e 152, m/e 137 (base peak) and lower mass peaks. The formation of some of the salient fragment ions has been given below.

<u>m/e 383 and m/e 380.</u> These fragment ions represent the loss of a methyl group and a molecule of water, respectively from the molecular ion, and are supported by metastables at 368.5 and 362.8.

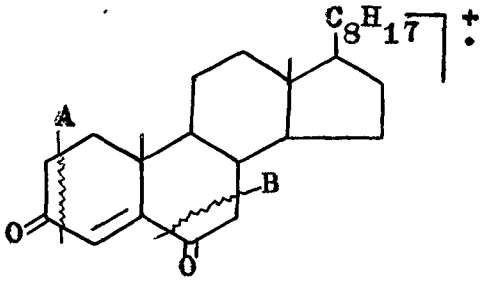
<u>m/e 370 ($C_{26}H_{42}O$).</u> The fragment ion m/e 370 represents the loss of CO from the molecular ion and is supported by a metastable peak at 343.9. The loss of CO may involve either the C3 or C6 carbonyl function or both. In either case, this loss involves the cleavage of a vinylic bond at one stage or the other. Several possibilities exist for the elimination of CO from the molecular ion. However, only one mechanism is being given below.



(XLVII')

m/e 370
($C_{26}H_{42}O$)

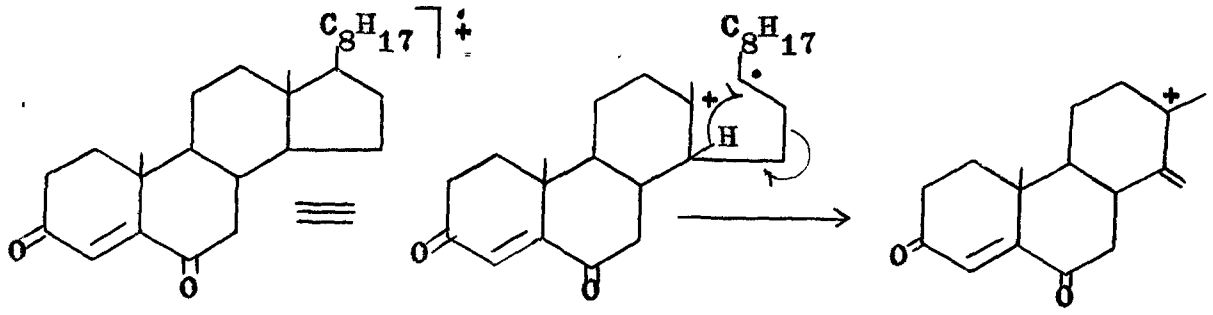
m/e 356 ($M-CH_2=C=O$; $C_{25}H_{40}O$). The fragment ion m/e 356 is best represented by the loss of a molecule of ketene from the molecular ion and this is supported by a metastable at 318.4. α,β-Unsaturated ketones, specially those having alkyl substituents at position 4 relative to the carbonyl group give intense $M-CH_2=C=O$ peak[145]. The C3 keto group at its relative position 4 is more substituted than the C6 keto group in this respect and therefore, is likely to contribute more in the expulsion of ketene molecule from the molecular ion. Thus fragmentation mode A is likely to contribute more than the mode B as shown below.



(XLVII')

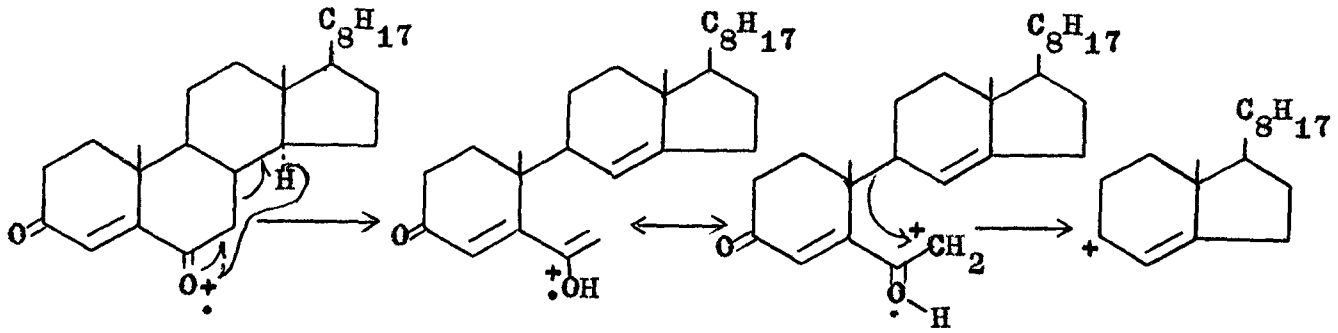
m/e 285. This fragment ion obviously results by the loss of the side chain (C_8H_{17}) from the molecular ion.

m/e 257. The fragment ion m/e 257 can be formulated as given below, which results by the elimination of the side chain and part of ring D.



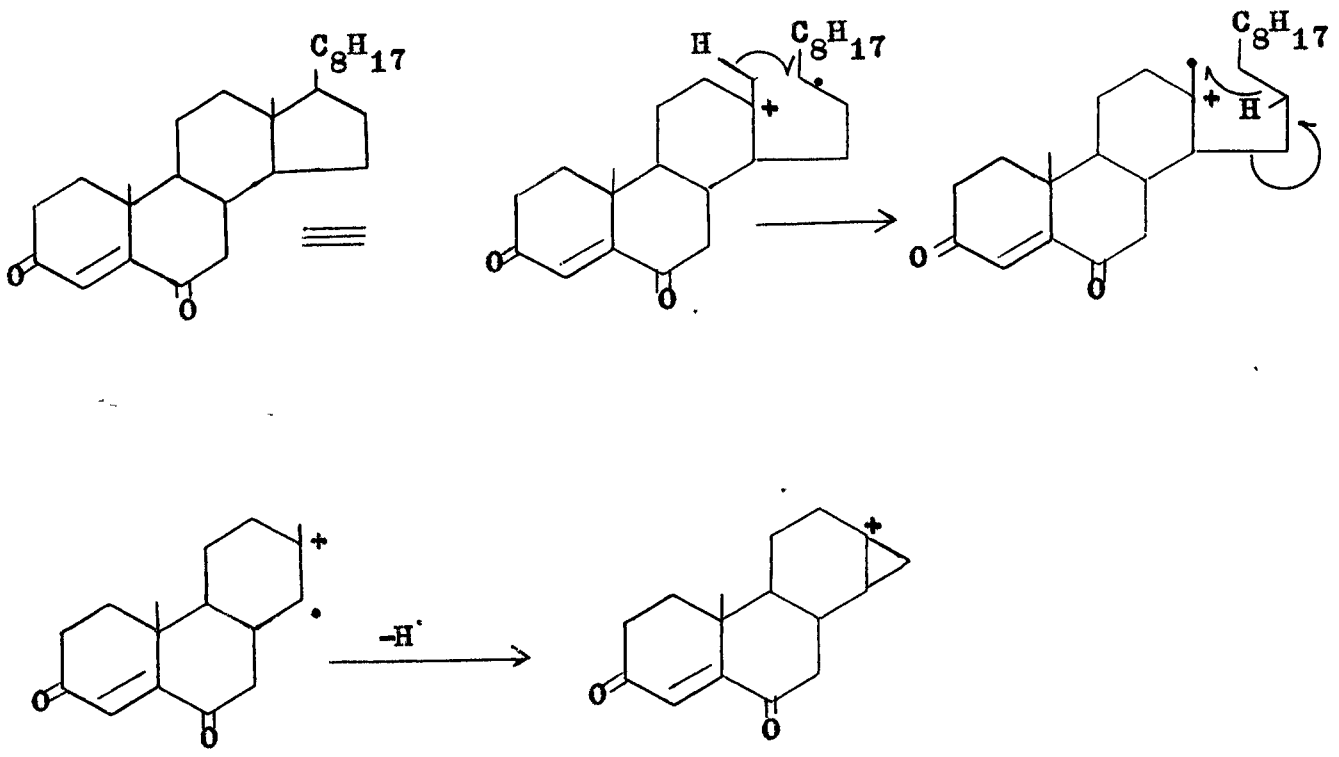
(XLVII") m/e 257

m/e 247 ($C_{18}H_{31}$). This hydrocarbon fragment ion is of common occurrence in the mass spectra of the cholestane derivatives. In the present case, its genesis has been rationalized according to pathway suggested below.



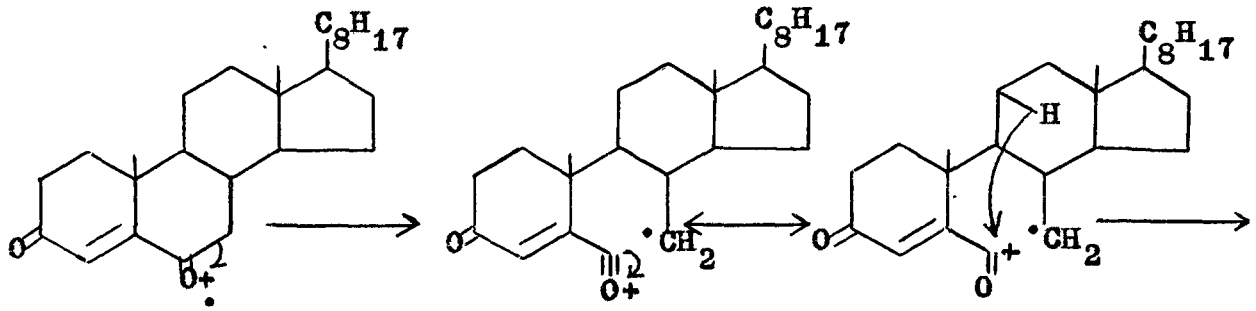
(XLVII') m/e 247

m/e 244 and m/e 243. These fragment ions can be rationalized according to scheme given below.

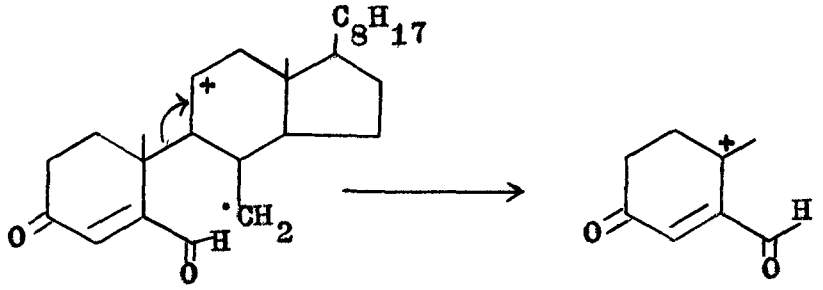


m/e 244 m/e 243

<u>m/e 137 (base peak; $C_8H_9O_2$)</u>. This is the base peak of the spectrum and its composition suggested that this must encompass both C3 and C6 carbonyl groups. A probable mechanism has been suggested below.



(XLVII')



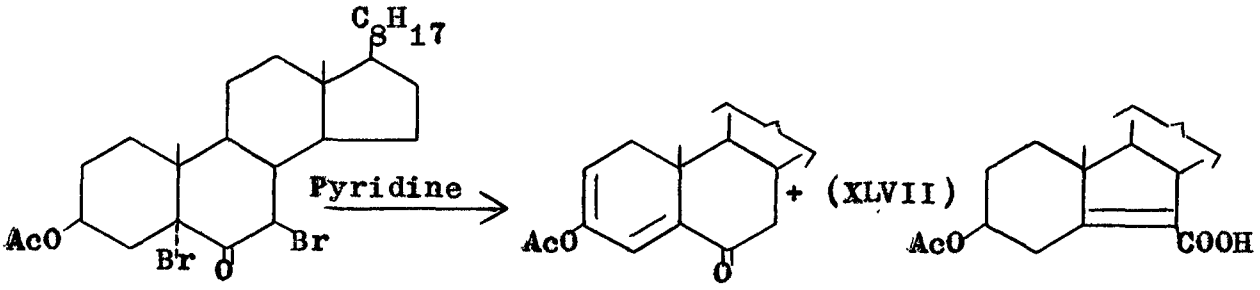
m/e 137
($C_8H_9O_2$)

From these observations it was evident that the compound, m.p. 123°, is cholest-4-ene-3,6-dione (XLVII) which was further confirmed by comparison with an authentic sample prepared according to the literature method[138]. Both the samples were found to be identical in all respects. Cholest-4-ene-3,6-dione (XLVII) in all probability is an artefact of 3-acetoxycholesta-2,4-dien-6-one (XLVI).

Dehydrobromination of 3β-acetoxy-5,7β-dibromo-5α-cholestan-6-one (XLV).

The dehydrobromination of 3β-acetoxy-5,7β-dibromo-5α-cholestan-6-one (XLV) was carried out in a manner described for the tribromide (CCIX). After usual work up of the reaction mixture, followed by column chromatography, 3-acetoxycholesta-2,4-dien-6-one (XLVI) and its artefact, cholest-4-ene-3,6-dione (XLVII) were obtained, comparable with the previously obtained samples in all respects.

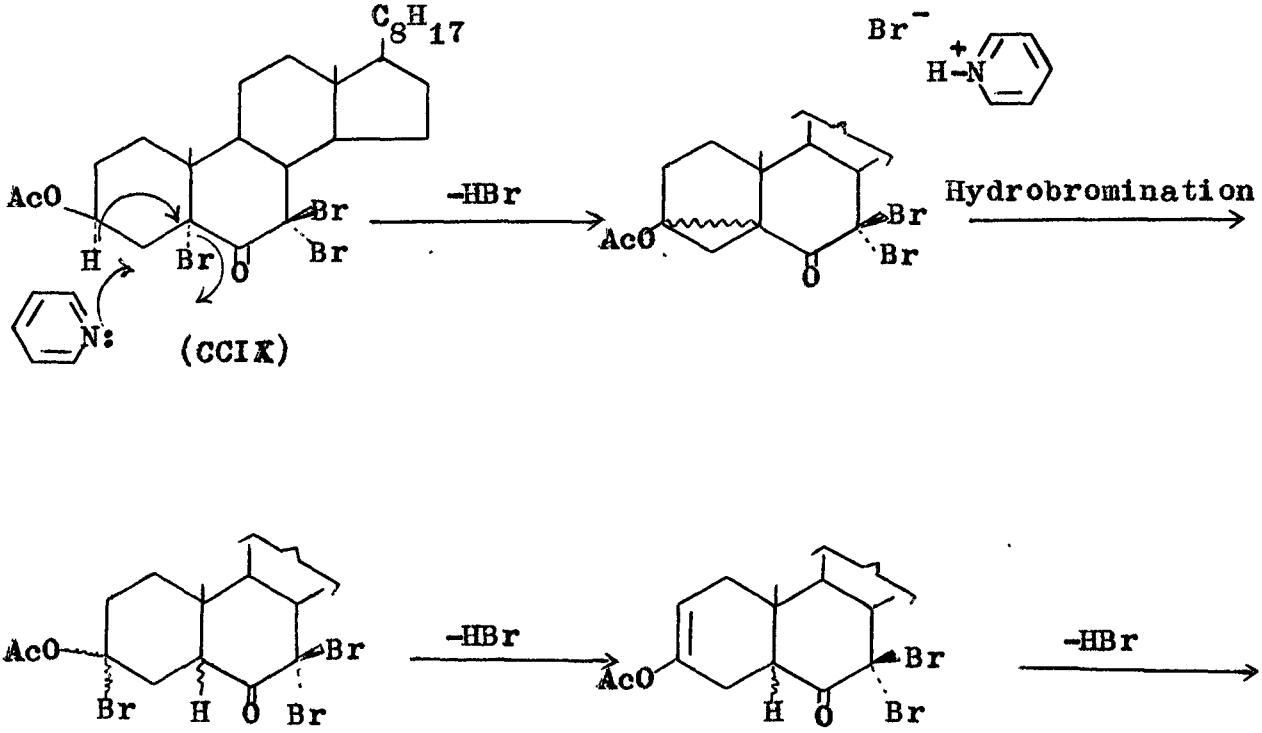
It is pertinent to mention that the dibromide (XLV) on dehydrobromination with pyridine was reported to furnish 3β-acetoxy-B-norcholest-5-en-6-carboxylic acid (LI) along with 3-acetoxycholesta-2,4-dien-6-one (XLVI)[78].

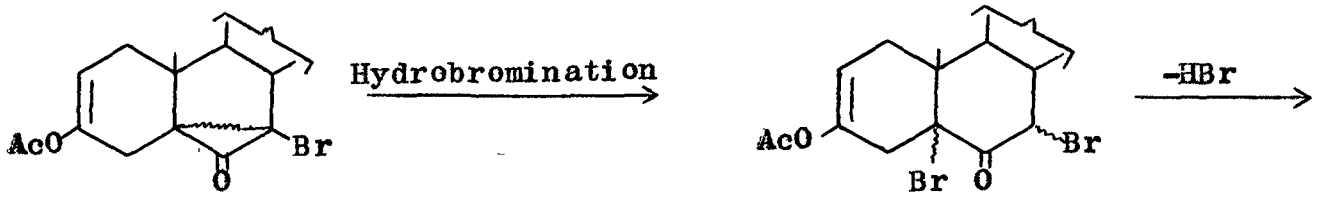


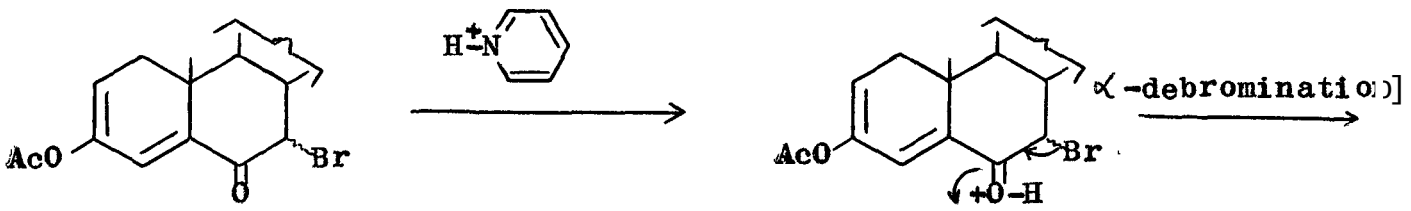
(XLV) (XLVI) (LI)

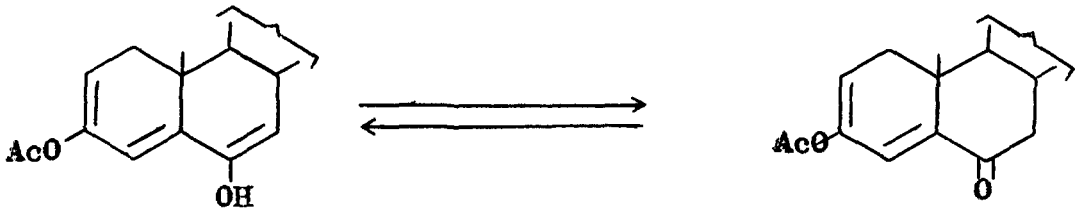
In our experiment, we were unable to isolate the B-nor carboxylic acid (LI). The acid (LI) if formed must have been in small quantity as to escape isolation.

Although the formation of 3-acetoxycholesta-2,4-dien-6-one (XLVI) from 3β-acetoxy-5,7β-dibromo-5α-cholestan-6-one (XLV) was reported earlier, its mechanism was not given in detail. The more intriguing is the formation of (XLVI) from the tribromide, 3β-acetoxy-5,7,7-tribromo-5α-cholestan-6-one (CCIX). The conversion (CCIX) ⟶ (XLVI) requires that α-debromination occurs at one stage or another under reaction conditions. A tentative mechanism is now being proposed to account for the formation of 3-acetoxycholesta-2,4-dien-6-one (XLVI) from the tribromide (CCIX).



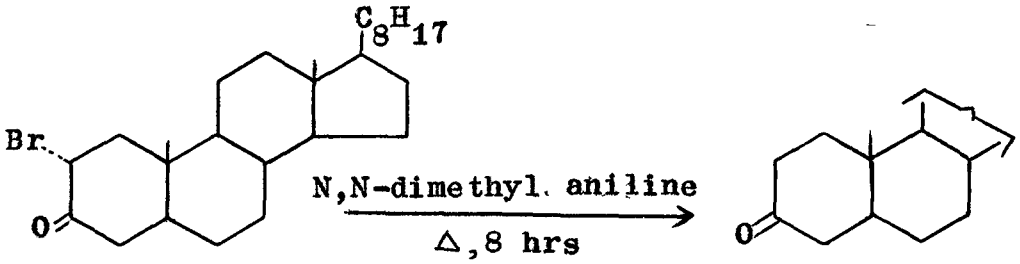

AcO
Br
O
Hydrobromination
AcO
Br
Br
O
-HBr


AcO
Br
O
H
N
AcO
Br
+O-H
∝-debromination]


AcO
OH
AcO
O

(XLVI)

It is pertinent to mention that a similar observation was made by Schwenk and Whitman[142] when they obtained cholestan-3-one (CCXIII) from 2α-bromocholestan-3-one (XXXVI) on heating the latter with N,N-dimethylaniline.

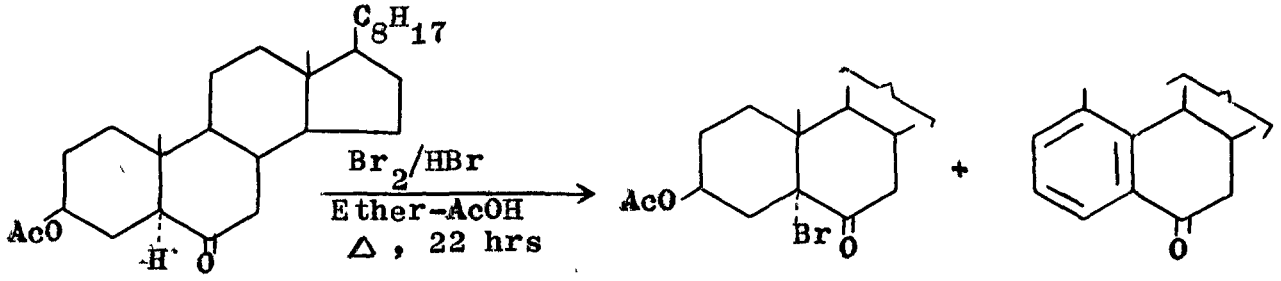


(XXXVI) (CCXIII)

In our continued efforts to prepare 3β-acetoxy-7α-bromo-5α-cholestan-6-one (CCVII) from 3β-acetoxy-5α-cholestan-6-one (CXV), the latter was heated under reflux with bromine and HBr (as catalyst) in the solvent system ether-acetic acid for 22 hours. After usual work up of the reaction mixture, followed by chromatography, 3β-acetoxy-5α-bromocholestan-6-one (CCXII), m.p. and mixed m.p. 162-163°[71] and compounds, m.pts. 140° and 172°, were obtained. The identity of the compounds, m.pts. 140° and 172° was made on the basis of spectral properties, elemental analysis and comparison with authentic sample where available.

Characterization of the compound, m.p. 140° as 1-methyl cholesta-1,3,5(10)-trien-6-one (CCXIV).

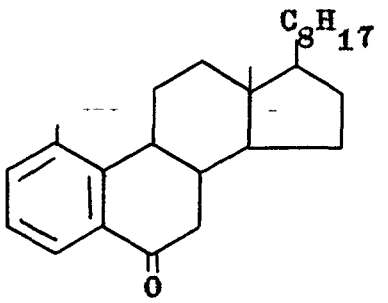
The compound, m.p. 140° (negative Beilstein test) analysed correctly for $C_{27}H_{40}O$ and its i.r. spectrum showed absorption bands at 3030w, 1585m(aromatic), 1680s cm^{-1} (C=C-C=O). There was no peak corresponding to acetate group either in the region 1730 or 1200 to 1250 cm^{-1}. The presence of an aromatic ring system conjugated with a carbonyl group was further substantiated by its u.v. spectrum (λ max. 255 nm; together with another band at 335 nm (weak).



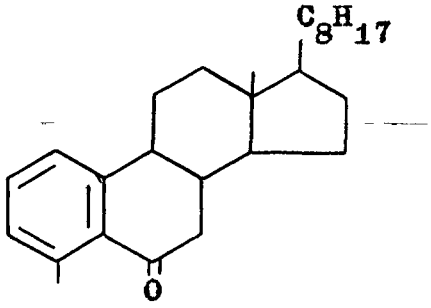
(CXV) (CCXII) (CCXIV)

The presence of an aromatic ring system was further revealed by the n.m.r. spectrum of the compound, m.p. 140°. The n.m.r. spectrum exhibited signals at δ 7.9. d,d (J=8 Hz, ortho coupled, and 3 Hz meta coupled, 1 proton, C4-H), 7.26m (2 protons, C2-H and C3-H), 2.43s (3 protons; C1-CH_3), 2.5m (merging with the methyl signal, -C(=O)-CH_2), 0.71 (C13-Me), 0.9 and 8.3 (other methyl

protons). The appearance of signals in the downfield region i.e. δ7.9 and 7.26 clearly indicated the presence of an aromatic ring in the compound under discussion. Two possible structures (CCXIV) and (CCXV) can be written for the compound, m.p. 140°.



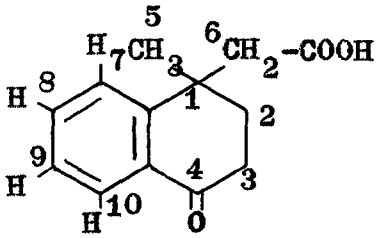
(CCXIV)



(CCXV)

A distinction between these structures (CCXIV) and (CCXV) was made with the help of n.m.r. spectrum. As is obvious from the structure (CCXIV), it has one β-proton with respect to the carbonyl function at C6 whereas in the other structure (CCXV), the β-position is occupied by a methyl group. The appearance of a signal at δ7.9 clearly indicated that there is a β-proton with respect to the carbonyl group compatible with the structure (CCXIV). In the other structure (CCXV) all the 3 aromatic protons are expected to be appearing as a multiplet at about δ7.3. On this basis the structure (CCXIV) has been assigned to the compound, m.p. 140°. A comparison of the n.m.r. values of the compound (CCXIV) was made with that of 1-methyl-1-

carboxymethyl-4-tetralone (CCXVI), where the β-proton to the carbonyl group appeared at downfield relative to other aromatic protons.

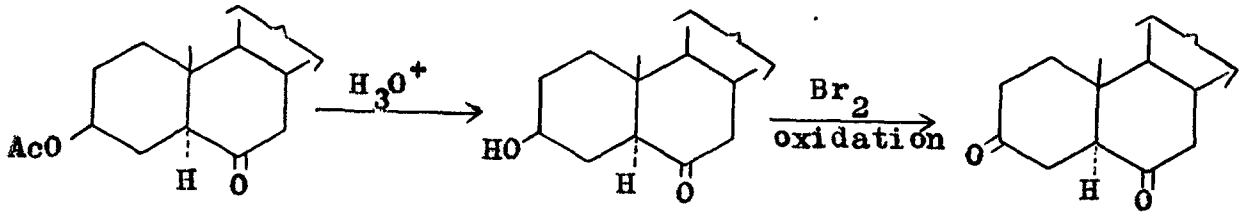


H(7), H(8), H(9) - δ7.41

H(10) δ8.02

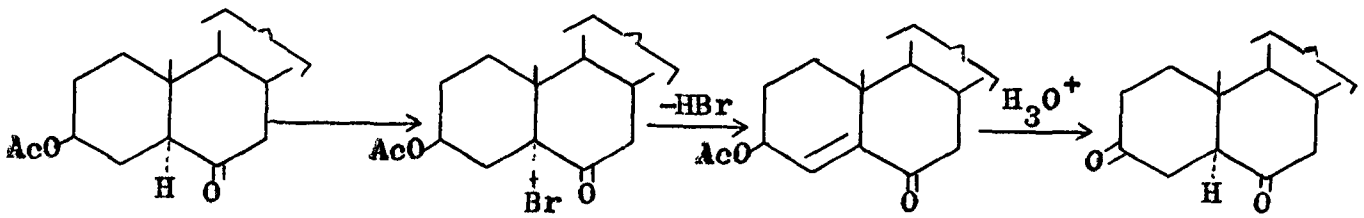
(CCXVI)

The compound, m.p. 172° (M^+ 400, $C_{27}H_{44}O_2$; ν C=O 1710 cm^{-1}; δ 2.3m (6 protons, C2-$\underline{H}_2$, C4-$\underline{H}_2$ and C7-$\underline{H}_2$), 0.96 (C10-Me), 0.71 (C13-Me), 0.92 and 0.83 (other methyl signals) was identified as 5α-cholestane-3,6-dione (CLXXXIX) by comparison with an authentic sample, prepared according to the literature procedure. The formation of the dione (CLXXXIX) may be rationalized according to the following sequence of reactions.

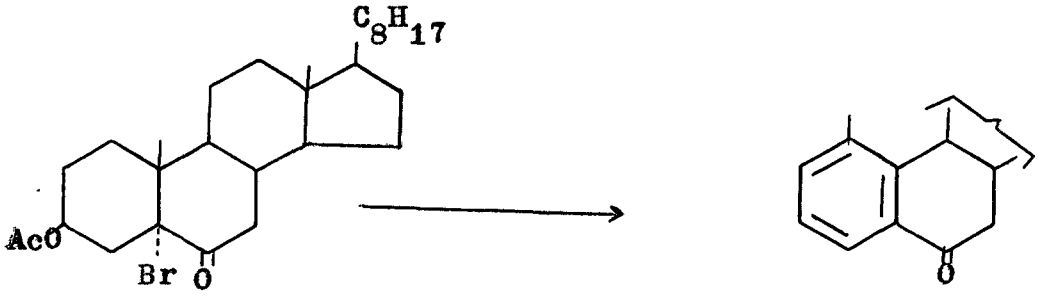


(CXV) (CLXXXIX)

or

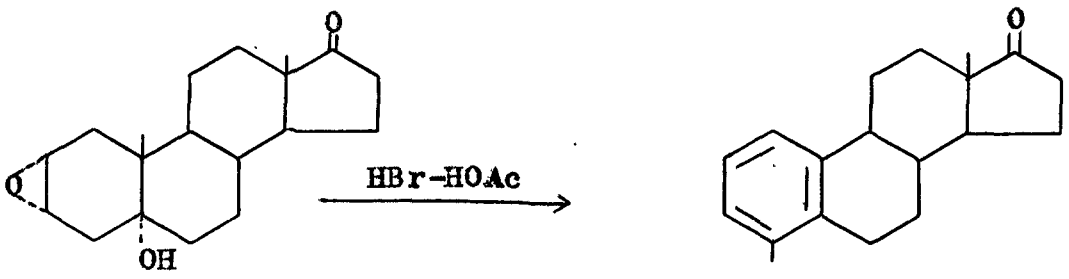


An account for the formation of the ring A aromatized product, 1-methyl-cholesta-1,3,5(10)-trien-6-one (CCXIV) from 3β-acetoxy-5α-cholestan-6-one (CXV) demands serious considerations. It has been experimentally realized that 3β-acetoxy-5α-bromocholestan-6-one (CCXII) gives rise to the aromatized product (CCXIV) under similar reaction conditions.

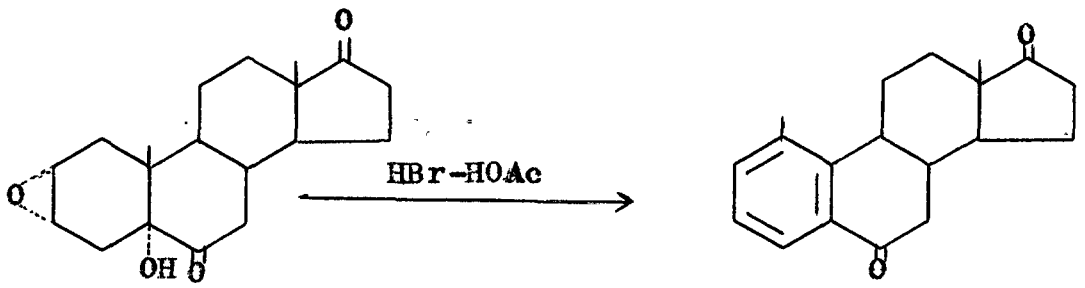


(CCXII) (CCXIV)

It has been recently observed by Hanson[94] that 2α,3α-epoxy-5α-hydroxyandrostan-17-one (LXXVIII) undergoes rearrangement to form 4-methylestra-1,3,5(10)-trien-17-one (LXXVII) whilst the corresponding 6-ketone (LXXIX) affords 1-methylestra-1,3,5(10)-triene-6,17-dione (LXXX) on treatment with HBr in glacial acetic acid.



(LXXVIII) (LXXVII)



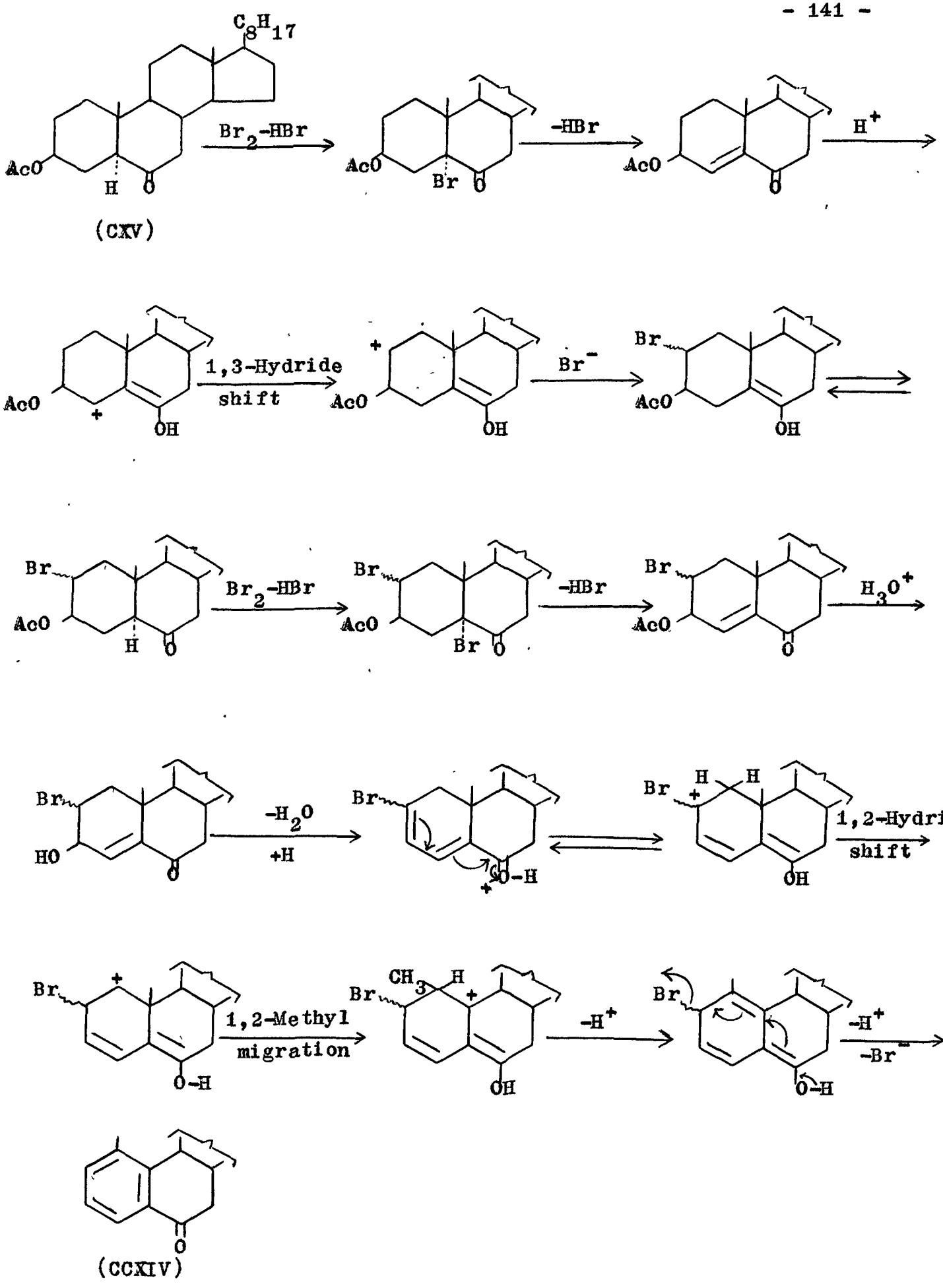
(LXXIX) (LXXX)

The presence of a 6-carbonyl function serves, as in the dienone-phenol rearrangement, to destabilize a C5-carbonium ion and prevents the formation of spirocyclic intermediates. This leads to aromatization via the alternative pathway of C10 $\longrightarrow$ C1 methyl migration.

Further the prerequisite for aromatization of ring A is the presence of three potential sites of unsaturation in rings A and B[93,98].

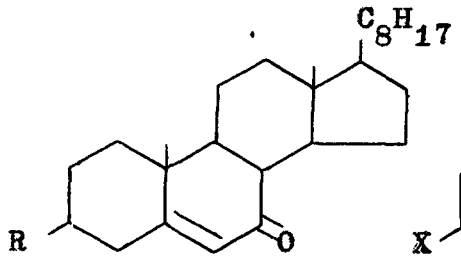
In view of these observations any postulated mechanism should avoid the formation of a C5-carbonium ion and subsequent spirocationic intermediate formation in the conversion (CXV) $\longrightarrow$ (CCXIV) and should involve such intermediate/s which have 3 potential sites of unsaturation in rings A and B.

The following mechanism, though tentative, is being proposed for the formation of the aromatized product (CCXIV).

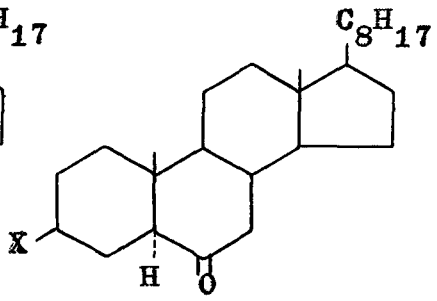

C8H17
AcO
H
O
Br2-HBr
Br
-HBr
H+
(CXV)
1,3-Hydride
shift
OH
Br-
Br2-HBr
H3O+
HO
-H2O
+H
1,2-Hydride
shift
1,2-Methyl
migration
CH3
-H+
-Br-
(CCXIV)

Baeyer-Villiger Oxidation of Steroidal Ketones

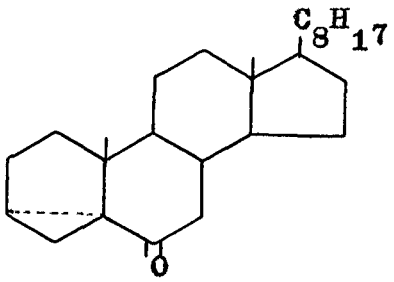
Previous work from these laboratories described the perbenzoic acid oxidation of 3β-acetoxycholest-5-en-7-one (CLXIII), cholest-5-en-7-one (CLXVIII), 3β-halo-5α-cholestan-6-ones (CLVII), (CLVIII) and (CLIX), 3α,5-cyclo-5α-cholestan-6-one (CLV) and 6β-bromocholest-4-en-3-one (CLXX).



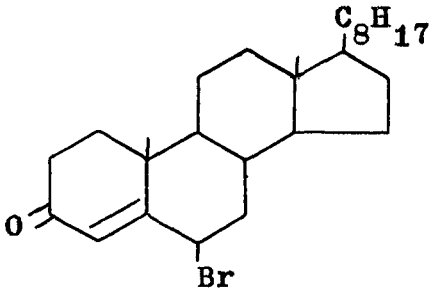
(CLXIII) R, OAc
(CLXVIII) R, H



(CLVII) X, Cl
(CLVIII) X, Br
(CLIX) X, I



(CLV)



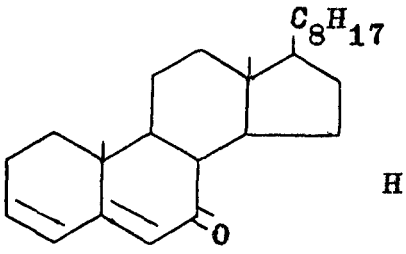
(CLXX)

In view of obtaining some interesting results and to extend the above work, cholesta-3,5-dien-7-one (CCXVII) was subjected to Baeyer-Villiger oxidation.

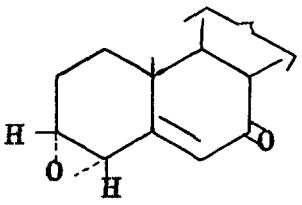
Reaction of cholesta-3,5-dien-7-one (CCXVII) with perbenzoic acid.

Reaction of the dienone (CCXVII) with perbenzoic acid using p-toluenesulphonic acid gave, after usual work up procedure and chromatography, two compounds, m.p. 136° and 205°. These were identified as 3α,4α-epoxycholest-5-en-7-one (CCXVIII) and 3α,4β-dihydroxycholest-5-en-7-one (CCXIX), respectively on the basis of chemical and spectral evidence.

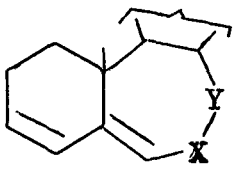
The compound (CCXVIII), m.p. 136°, analysed correctly for $C_{27}H_{42}O_2$ and its mass spectrum gave molecular ion peak at m/e 398 ($C_{27}H_{42}O_2$). From elemental composition it is apparent that only one oxygen atom has been introduced during the reaction. This leads to several possibilities and the product may be formulated as the epoxide (CCXVIII), the enol lactone (CCXXI), or the α,β-unsaturated lactone (CCXXII).



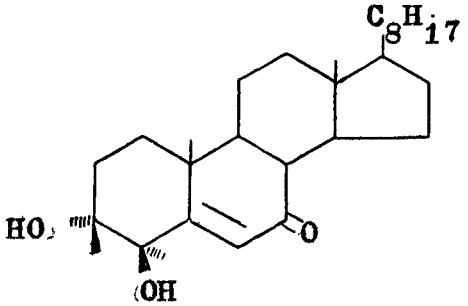
(CCXVII)



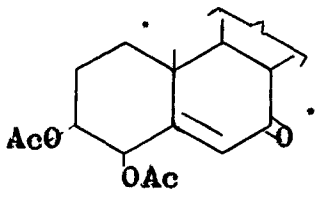
(CCXVIII)



	X	Y
(CCXXI)	O	CO
(CCXXII)	CO	O



(CCXIX)



(CCXX)

The u.v. spectrum of the product (λmax. 241 nm, log ϵ 3.46), showed the presence of an α,β-unsaturated ketonic function. The presence of an α,β-unsaturated ketonic group was further supported by its i.r. spectrum. The i.r. spectrum showed peaks at 1680 (C=C-C=O), 1638 (-C=C-), 870 and 775 cm^{-1} (epoxide ring)[143]. These spectral properties clearly discarded the ϵ-lactone structures (CCXXI) and (CCXXII). Further the n.m.r. spectrum of the compound, m.p. 136°, gave a signal at δ5.95s, integrating for 1 proton. This was assigned to a vinylic proton (C6-H) as in the epoxide (CCXVIII), no other vinylic proton was indicated. Further an unresolved multiplet centred at δ3.38 integrating for 2 protons was ascribable to C3 and C4-protons. The narrowness of the peak ($W\frac{1}{2} \backsim$ 5 Hz) shows small coupling which indicates that the C3-H is equatorial (β) and that C4-H though axial (β) has small coupling with C3-H (equatorial proton) only. From this it is obvious that the epoxide oxygen (C3 $\overset{O}{\diagup\diagdown}$ C4) must be α-oriented. This is in line with the general observation that the reagents prefer to attack a steroidal molecule from less hindered α-side[144].

The n.m.r. spectrum of the ϵ-lactones (CCXXI) or (CCXXII) will give signals for 3 vinylic protons. Further in structure (CCXXII) C8 proton will appear as a doublet of doublets at about δ4.2. From the consideration of above spectral properties it is reasonable to assign the epoxide structure (CCXVIII) to the compound, m.p. 136°.

The compound, (CCXIX), m.p. 205°, analysed correctly for $C_{27}H_{44}O_3$ and its mass spectrum gave molecular ion peak at m/e 416 ($C_{27}H_{44}O_3$). From the elemental composition it is indicated that (CCXIX) may be the product of hydrolysis of the epoxide (CCXVIII; $C_{27}H_{42}O_2 + H_2O$). This indeed is the case, as has been shown by the conversion of (CCXVIII) into (CCXIX) by mild hydrolysis. The u.v. spectrum of the diol (CCXIX)(λ max. 244 nm; log ϵ 3.36) showed the presence of an α,β-unsaturated ketonic group. Its i.r. spectrum showed peaks at 3360 (OH), 1680 (C=C-C=O), 1640(sh) (C=C), 1075, 1022 and 1015 cm^{-1} (-C-O).

The n.m.r. spectrum of (CCXIX) showed a sharp singlet at δ5.75 integrating for 1 proton and was assigned to C6-vinylic proton. An unresolved multiplet centred at δ4.05 integrating for 2 protons was ascribable to C3 and C4 protons. The magnitude of splitting of this peak ($W_{\frac{1}{2}}$ = 5 Hz) showed that both the protons are equatorial (C3β- and C4α-), thus indicating that C3- and C4-hydroxy groups are axial (C3α-OH and C4β-OH). From mechanistic considerations it is to be expected that the epoxide ring will

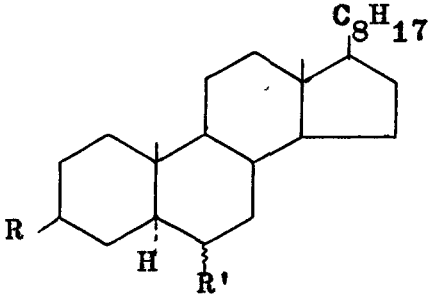
open during hydrolysis to give trans diaxial diol such as (CCXVIII) $\longrightarrow$ (CCXIX)[144].

Though not very pertinent, a cursory comparison of the n.m.r. spectrum of (CCXIX) was made with those of 5α-cholestane-3β,6α-diol (CCXXIII) and 5α-cholestane-3β,6β-diol (CCXXIV) from the chemical shift point of view of H-C-OH protons. In (CCXXIII) both the protons (C3α- and C6β-protons) being axial appeared as a broad peak centred at δ3.3. In (CCXXIV), C3α-H being axial appeared as a broad peak centred at δ3.66 whereas C6α-H being equatorial appeared as a relatively 'narrow' multiplet centred at δ3.76 (lower field).

As expected, the diol (CCXIX) with acetic anhydride and pyridine was converted into the diacetate, 3α,4β-diacetoxy-cholest-5-en-7-one (CCXX). The diacetate (CCXX) in its mass spectrum gave molecular ion peak at m/e 500 and analysed correctly for $C_{31}H_{48}O_5$. Its u.v. spectrum, as expected, showed absorption maxima at 241 nm (log ϵ 3.63), supporting the α,β-unsaturated carbonyl chromophore. The i.r. spectrum of (CCXX) showed peaks at 1755(sh), 1740 (ester carbonyl), 1680 (-C=C-CO-), 1640(sh) (-C=C-) and 1235 cm^{-1} (acetate). The n.m.r. spectrum of (CCXX) gave a singlet (1 proton) at δ5.9 ascribable to C6-vinylic proton. The C3 and C4 proton signals were well separated and not merged together as in the case of diol (CCXIX). A doublet

(J = 3 Hz) at δ5.22 was assigned to C4α-H (equatorial) and a broader peak at δ4.96 was assigned to C3β-H (equatorial), since C3 proton interacts with C2-methylene and C4-methine protons (3 protons interaction compared with 1 proton interaction of C4-H). The presence of two acetate groups was revealed by two sharp singlets at δ2.05 and 2.02 (3 protons each).

Chemical shifts of C3 and C4 protons of (CCXX) were compared with those of C3 and C6 protons of the diacetates 5α-cholestane-3β,6α-diol diacetate (CCXXV) and 5α-cholestane-3β, 6β-diol diacetate (CCXXVI). In (CCXXV) both C3 and C6 protons being axial appeared as a broad multiplet centred at δ4.64. On the other hand in (CCXXVI) C3α-H being axial appeared as a broad peak centred at δ4.7 whereas, C6α-H being equatorial appeared as a relatively 'narrow' peak centred at δ4.9 (lower field)[141].

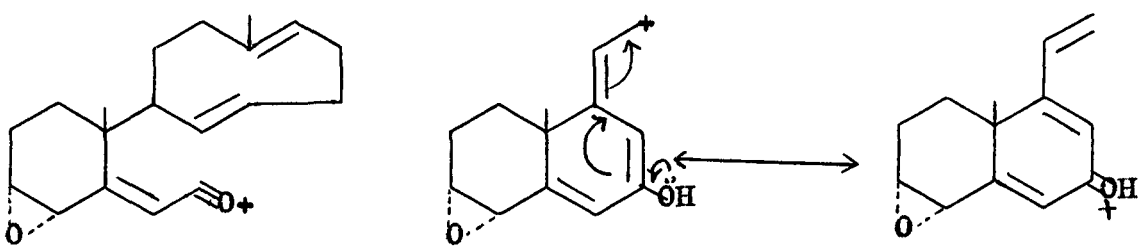


	R	R'
(CCXXIII)	OH	α-OH
(CCXXIV)	OH	β-OH
(CCXXV)	OAc	α-OAc
(CCXXVI)	OAc	β-OAc

The effect of different substituents at C3 and C4 as in (CCXVIII), (CCXIX) and (CCXX) on the C19-H signal is obvious. The C10-methyl signals appeared at δ 1.08, 1.34 and 1.31 in (CCXVIII), (CCXIX) and (CCXX), respectively.

The mass spectrum of 3α,4α-epoxycholest-5-en-7-one (CCXVIII) (Fig. 3) showed strong molecular ion peak at m/e 398 (base peak), with other salient peaks at m/e 383 ($M-CH_3$), m/e 380 ($M-H_2O$), m/e 370 (M-CO), m/e 285 ($M-C_8H_{17}$ side chain), m/e 203 ($C_{13}H_{15}O_2$), m/e 190 ($C_{12}H_{14}O_2$), m/e 177 ($C_{11}H_{13}O_2$) and m/e 150 ($C_9H_{10}O_2$).

The spectrum of (CCXVIII) can easily be related with that of the starting dienone (CCXVII)[cf.147]. The presence of 3α,4α-epoxy group does not seem to make notable difference on the fragmentation pattern. The formation of fragment ions m/e 285, m/e 203, m/e 190, m/e 177 and m/e 150 can be shown as for the ions m/e 269, m/e 187, m/e 174, m/e 161 and m/e 134, respectively in the mass spectrum of the dienone (CCXVII) and can be formulated as shown below:



m/e 285 ($C_{19}H_{25}O_2$)

m/e 203 ($C_{13}H_{15}O_2$)

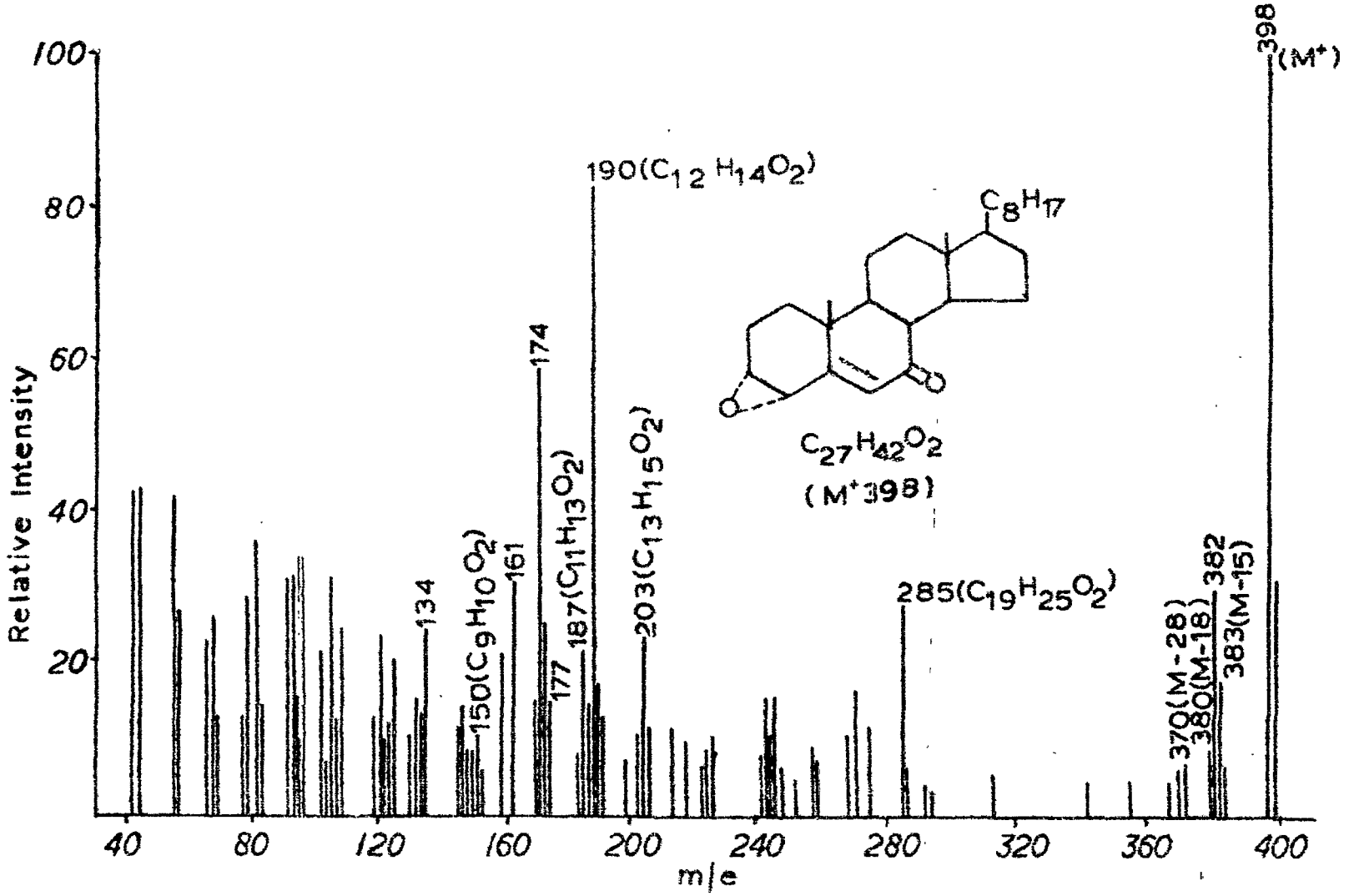
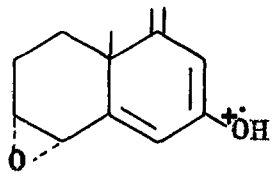
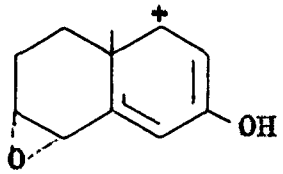

100
80
60
40
20
Relative Intensity
398
(M+)
190(C12H14O2)
C8H17
174
134
150(C9H10O2)
161
177
187(C11H13O2)
203(C13H15O2)
285(C19H25O2)
370(M-28)
380(M-18)
382
383(M-15)
C27H42O2
(M+398)
40
80
120
160
200
240
280
320
360
400
m/e

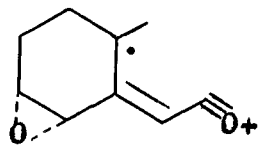
Figure 3



m/e 190
($C_{12}H_{14}O_2$)



m/e 177
($C_{11}H_{13}O_2$)



m/e 150
($C_9H_{10}O_2$)

It is pertinent to point out that in the mass spectrum of the epoxide (CCXVIII) peaks at m/e 382, m/e 187, m/e 174 and m/e 161, typical of the dienone (CCXVII) were also observed. All the standard care was taken in the purification of the epoxide (CCXVIII) and its n.m.r. and i.r. spectra do not show the presence of the dienone (CCXVII). It is therefore reasonable to suggest that under electron impact the epoxy oxygen is eliminated to give the dienone species which undergoes fragmentation in the usual manner. However, this suggestion should be considered with caution as trace amounts of dienone (CCXVII) present as impurity in the epoxide (CCXVIII) can not be completely ruled out.

The presence of two vicinal hydroxyl groups in 3α,4β-dihydroxycholest-5-en-7-one (CCXIX)(Fig. 4) makes the spectrum a bit more complicated than that of (CCXVIII). However, comparable peaks are observed in the spectrum of (CCXIX) and their rationalization is possible relative to (CCXVIII). The mass spectrum of (CCXIX) showed a strong molecular ion peak at m/e 416 (base peak; $C_{27}H_{44}O_3$); other salient peaks were observed at m/e 401($M-CH_3$),

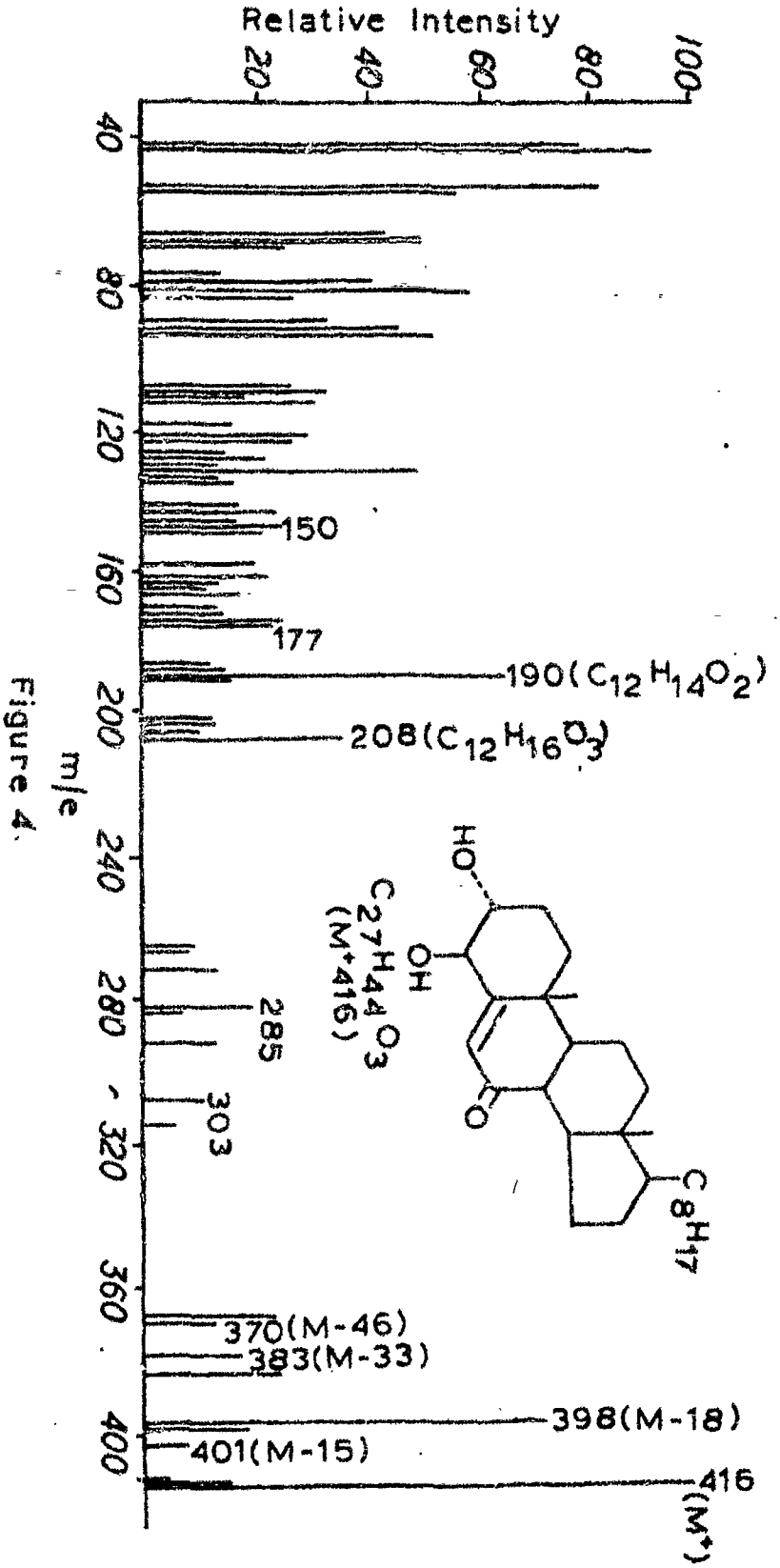
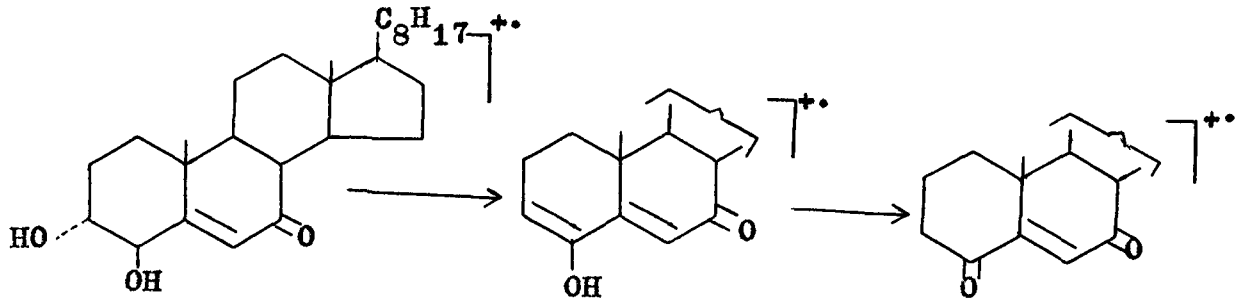

Relative Intensity
20
40
60
80
100
40
80
120
160
200
240
280
320
360
400
m/e
150
177
190($C_{12}H_{14}O_2$)
208($C_{12}H_{16}O_3$)
285
303
370(M-46)
383(M-33)
398(M-18)
401(M-15)
416
(M+)
HO
OH
O
$C_{27}H_{44}O_3$
(M+416)
C_8H_{17}

Figure 4.

m/e 398 ($M-H_2O$), m/e 383 ($M-H_2O + CH_3$), m/e 370 ($M-H_2O + CO$), m/e 303 ($M-C_8H_{17}$ side chain), m/e 285 ($M-H_2O + C_8H_{17}$), m/e 208 ($C_{12}H_{16}O_3$), m/e 190 ($C_{12}H_{14}O_2$), m/e 177 and m/e 150.

Precise formulation of the ion m/e 398 ($M-H_2O$) is difficult in the absence of mass spectra of appropriate deuterated analogues of (CCXIX). The loss of water molecule from the molecular ion may involve 1,3-elimination (C3α-OH and C1-H/C4β-OH and C2-H) as well as 1,4-elimination involving C4β-OH and C1-H as in the case of elimination of water molecule from cyclohexanol[145]. It may be assumed that in the presence of a conjugated system such as in (CCXIX), the loss of water molecule may involve 1,2-elimination (say for example C3α-OH and C4α-H) to give a stable system tentatively suggested as (a).



(CCLXII) (a)

m/e 398

The fragment ion m/e 208 ($C_{12}H_{16}O_3$) may be formulated as (b) and the loss of a molecule of water from this will give the ion (c) m/e 190 ($C_{12}H_{14}O_2$).

(b)
m/e 208 ($C_{12}H_{16}O_3$)

(c)
m/e 190 ($C_{12}H_{14}O_2$)

Other fragment ions such as m/e 177 and m/e 150 may be formulated as (d) and (e) respectively.

(d)
m/e 177

(e)
m/e 150

The mass spectrum of 3α,4β-diacetoxycholest-5-en-7-one (CCXX)(Fig. 5) is much more complicated than that of (CCXVIII). The mass spectrum shows a very weak molecular ion peak at m/e 500 ($C_{31}H_{48}O_5$), the other salient peaks are at m/e 440 (M-CH_3COOH), m/e 398 (440-CH_2=C=O; $C_{27}H_{42}O_2$), m/e 396 (440-CO_2; $C_{28}H_{44}O$), m/e 383 (398-CH_3); m/e 381 (396-CH_3), m/e 380 (398-H_2O), m/e 370 (398-CO), m/e 327 (440-C_8H_{17} side chain), m/e 232 ($C_{14}H_{16}O_3$), and m/e 188 ($C_{13}H_{16}O$).

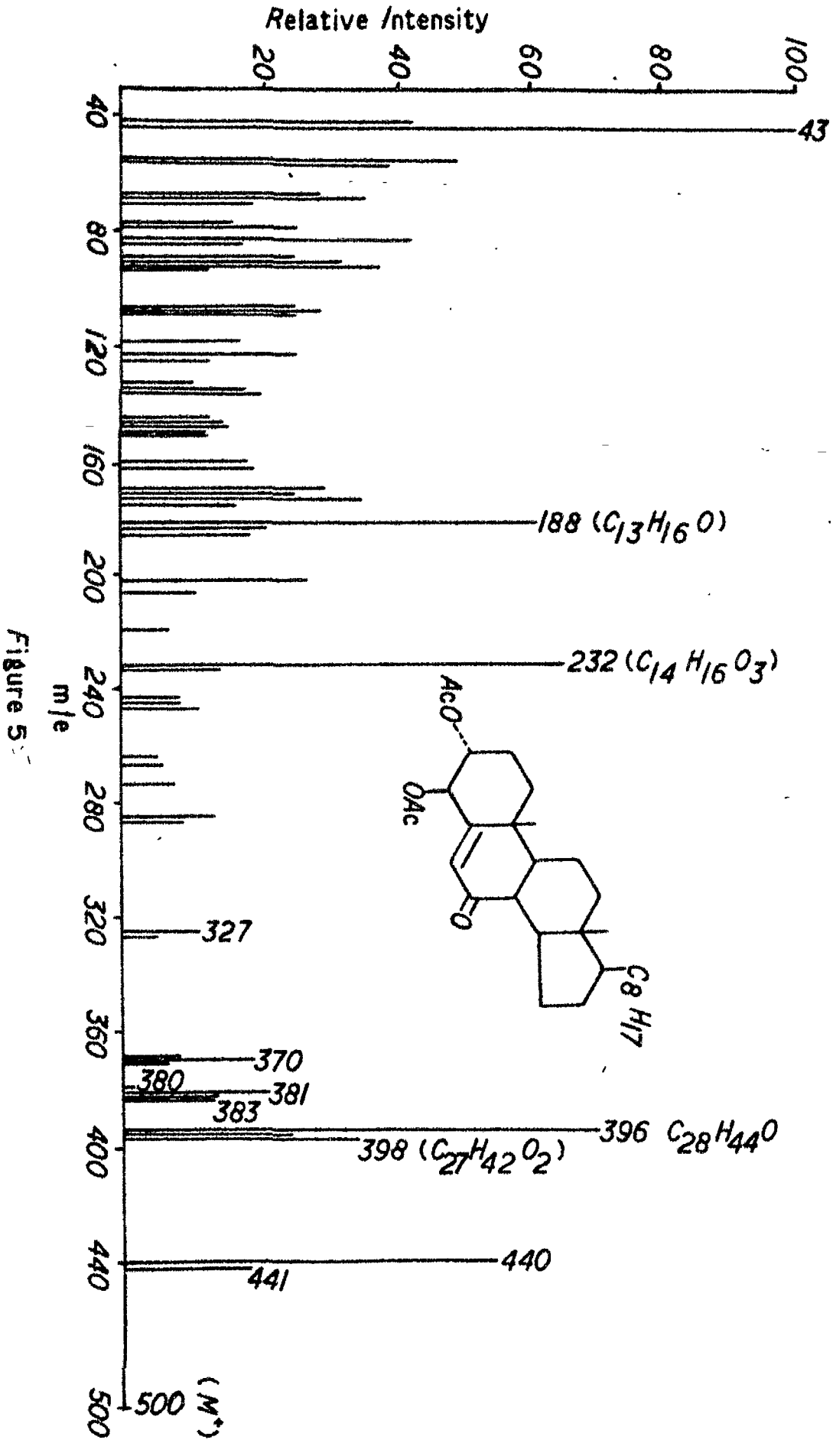
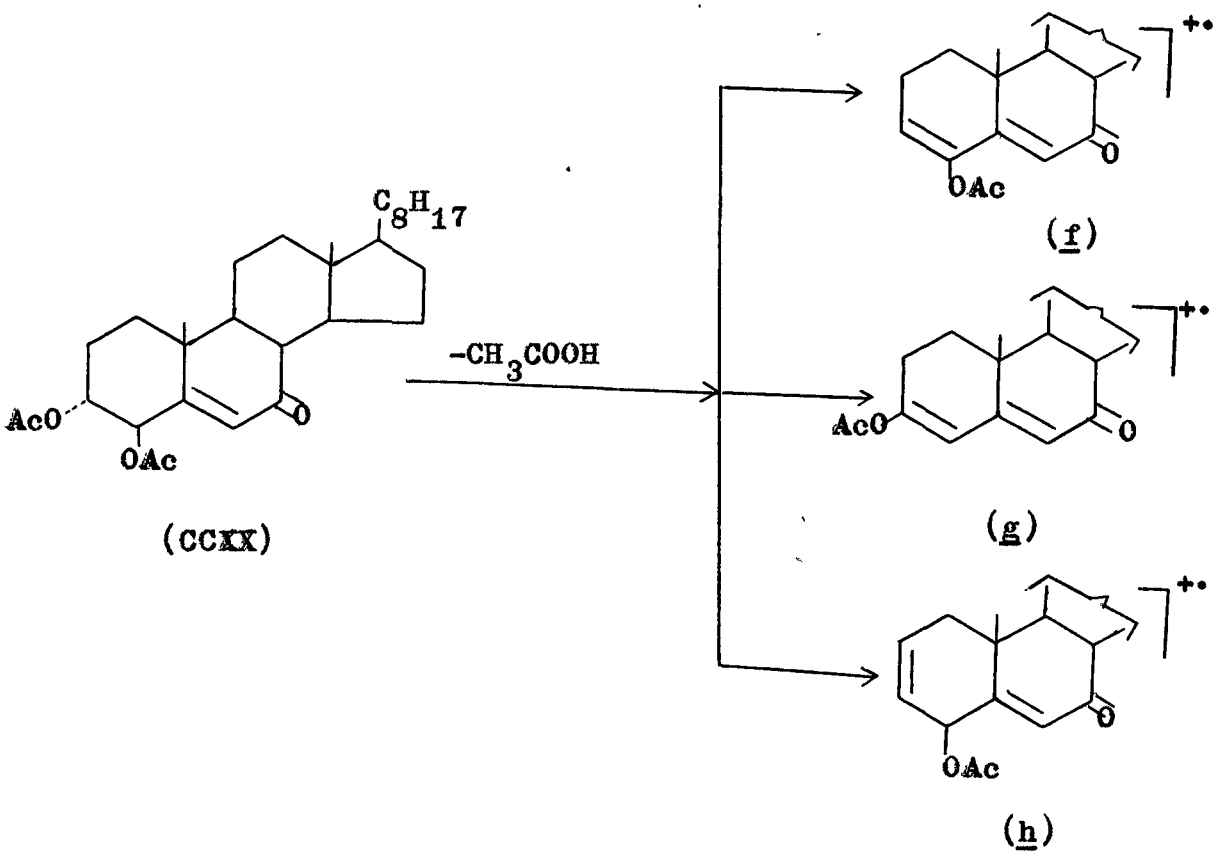

Relative Intensity
20
40
60
80
100
40
80
120
160
200
240
280
320
360
400
440
500
m/e
43
188 ($C_{13}H_{16}O$)
232 ($C_{14}H_{16}O_3$)
327
370
380
381
383
396 $C_{28}H_{44}O$
398 ($C_{27}H_{42}O_2$)
440
441
500 (M^+)
AcO
OAc
O
C_8H_{17}

Figure 5

The loss of acetic acid is typical of acetates[146] and this loss occurs predominantly by 1,2-elimination. From (CCXX) the loss of a molecule of acetic acid may involve 3α-acetate + 4α-H or/and 4β-acetate + 3β-H. In either case a double bond between C3-C4 will be created thus extending the conjugation. The third possibility involving 3α-acetate and C2-H may also be considered.

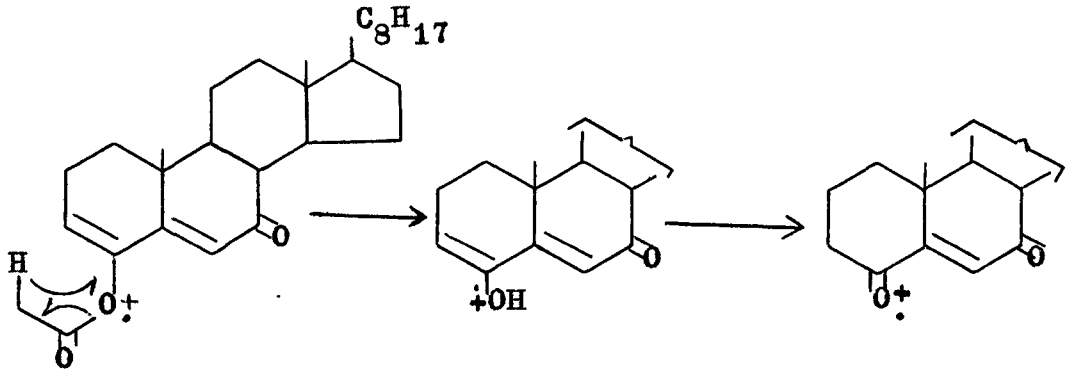


(CCXX)

For the present discussion, ion (f) has been arbitrarily chosen to explain the breakdown pattern (though ion g could be used with equal effectiveness for this purpose. Ion h has not been given much consideration as conjugated systems like f or g is more likely to dominate). The fragment ion m/e 440 ($M-CH_3COOH$) does not show further loss of acetic acid and there appears to be no rationale for such a loss, instead, a molecule of CO_2 is lost to give the fragment ion m/e 396 ($C_{28}H_{44}O$). Ion f has been used in the following schemes to show the formation of salient peaks.

m/e 398

From the composition ($C_{27}H_{42}O_2$) it appears that it is derived from the ion m/e 440 by the loss of a molecule of ketene[147]. This assumption was supported by a metastable peak at 360.

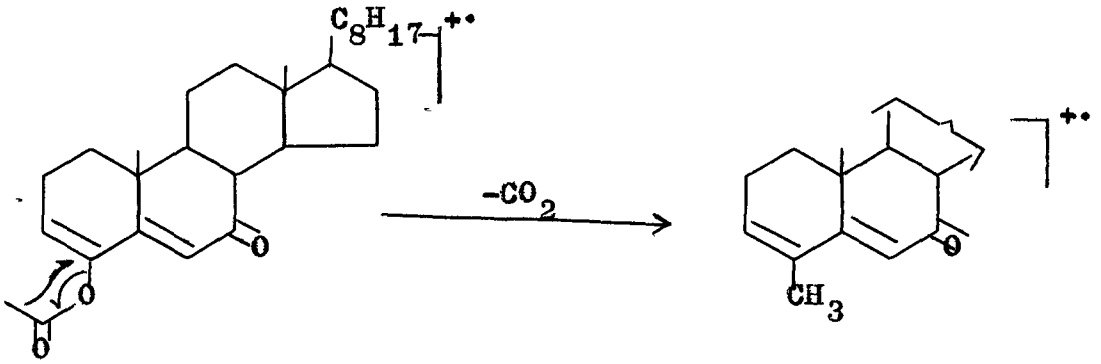


(f)
m/e 440

(i)
m/e 398 ($C_{27}H_{42}O_2$)

m/e 396

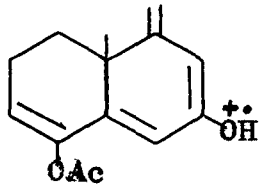
The composition $C_{28}H_{44}O$ suggests that a molecule of CO_2 is lost from the ion 440 to give the fragment ion m/e 396.



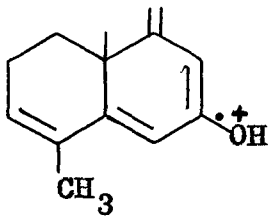
(f)
m/e 440

(j)
m/e 396 ($C_{28}H_{44}O$)

Fragment ions m/e 232 and m/e 188 from (CCXX) have been formulated as (k) and (l), respectively.



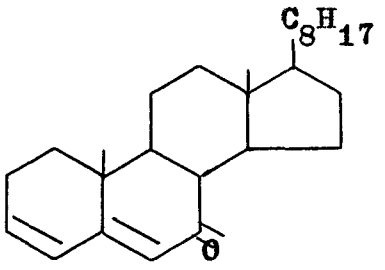
(k)
m/e 232 ($C_{14}H_{16}O_3$)



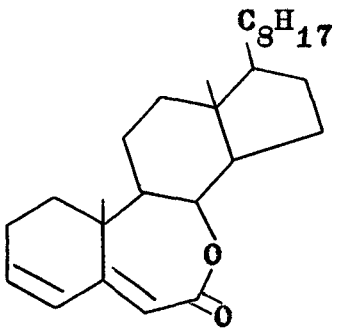
(l)
m/e 188 ($C_{13}H_{16}O$)

Reaction of cholesta-3,5-dien-7-one (CCXVII) with performic acid.

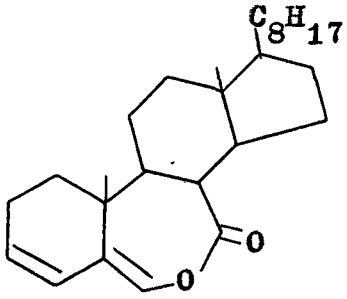
As mentioned earlier the reaction of cholesta-3,5-dien-7-one (CCXVII) with perbenzoic acid provided 3α,4α-epoxycholest-5-en-7-one (CCXVIII) and its artefact, 3α,4β-dihydroxycholest-5-en-7-one (CCXIX) and none of the expected ε-lactones, 7a-oxa-B-homocholesta-3,5-dien-7-one (CCXXII) and 7-oxa-B-homocholesta-3,5-dien-7a-one (CCXXI) or the products derived from them was obtained.



(CCXVII)



(CCXXII)



(CCXXI)

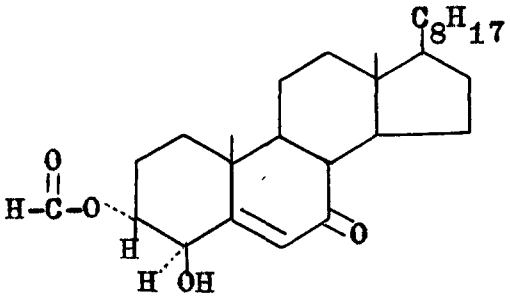
In order to obtain the ε-lactones (CCXXI) and (CCXXII), the dienone (CCXVII) was treated with the varying quantities of performic acid for different lengths of time. Invariably, this reaction, after usual work up and column chromatography provided the epoxide (CCXVIII), the diol (CCXIX), 3α-formyloxy-4β-hydroxy-cholest-5-en-7-one (CCXXVII), m.p. 162°, and cholest-5-ene-3,7-dione (CCXXX), m.p. 165°; the relative amounts of these products

depended largely upon the experimental conditions. The homogeneity of these products was ensured by t.l.c. using different solvent systems.

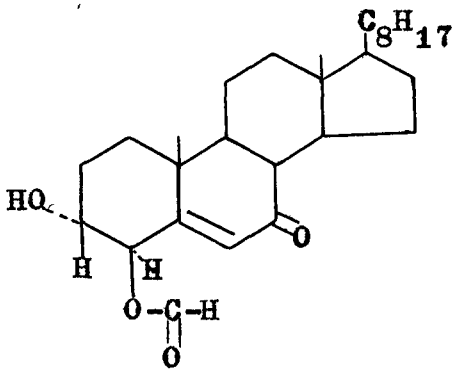
Characterization of the compound, m.p. 162° as 3α-formyloxy-4β-hydroxycholest-5-en-7-one (CCXXVII).

The compound, m.p. 162° analysed correctly for $C_{28}H_{44}O_4$. From the elemental composition it is evident that 3 oxygen atoms have been introduced during the reaction. The i.r. spectrum of the compound, m.p. 162° gave peaks at 3455(OH), 1735(-$\overset{O}{\overset{\|}{C}}$-O-), 1685 (-$\overset{O}{\overset{\|}{C}}$-C=C-), 1620 (C=C), 1185 (formate ester), 1075 and 1020 cm^{-1} (C-O-). The presence of an α,β-unsaturated carbonyl group was further substantiated by the u.v. spectrum of the compound (λ max. 242 nm, log ε 3.48).

To accommodate the above i.r. spectral values two possible structures (CCXXVII) and (CCXXVIII) for the compound, m.p. 162° could be suggested which can possibly arise from the reaction conditions.



(CCXXVII)

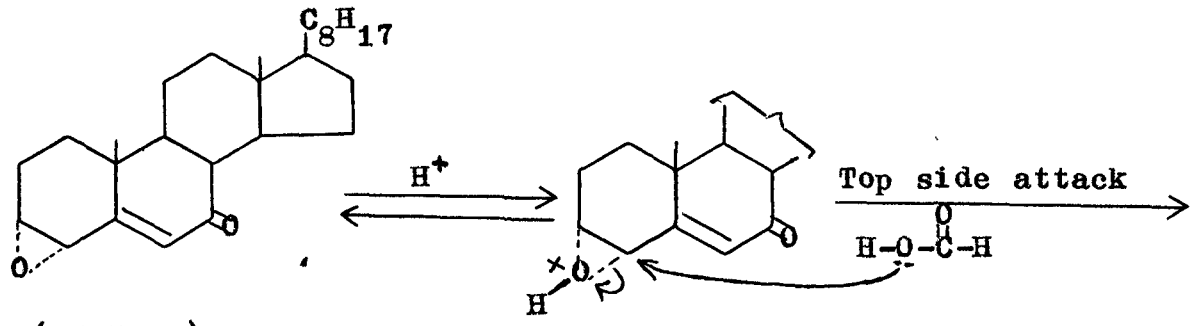


(CCXXVIII)

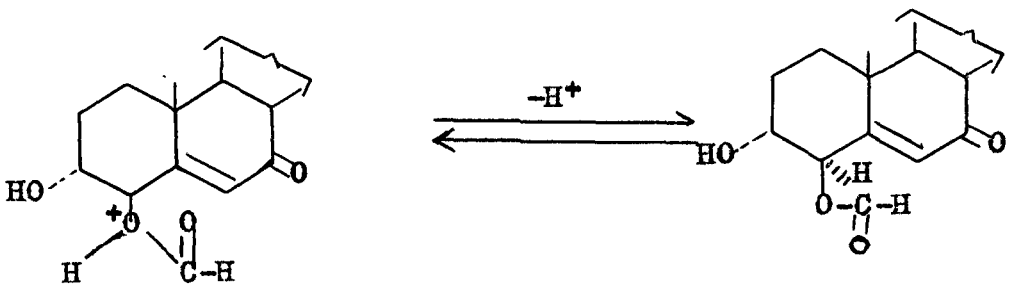
The n.m.r. spectrum of the compound, m.p. 162° gave signals at δ 8.1s (1 proton, $-O-\overset{O}{\overset{\|}{C}}-\underline{H}$), 5.8s (1 proton, C6-$\underline{H}$, vinylic proton), 5.26br (1 proton, $W\frac{1}{2}$ 8 Hz, $\underline{H}C3-O-\overset{O}{\overset{\|}{C}}-$, equatorial, β-oriented), 4.6br s(C4-O$\underline{H}$, disappeared on addition of D_2O), 4.2d like (1 proton, J=3.5 Hz; $W\frac{1}{2}$ 5 Hz, $\underline{H}$-C4-OH, equatorial, α-oriented), 1.4s (3 protons, C10-Me), 0.7s (3 protons, C13-Me), 0.93 and 0.85 (other methyl signals). On addition of D_2O, only the signal at δ4.6 disappeared and there was no significant change in any other part of the spectrum. The chemical shifts and magnitude of splitting for C3 and C4 protons clearly indicated that both of them are equatorially oriented. The downfield signal at δ5.26 should be ascribed to a proton attached to the carbon carrying the formate group, and the one at δ4.2 should be ascribable to the proton attached to the carbon carrying a hydroxyl group. From the shape and magnitude of splitting of the signal at δ5.26, it is evident that this one is interacting with at least 3 vicinal protons, whereas the signal at δ4.26 (doublet like) is interacting with one proton, as in the structure (CCXXVII). In the alternate structure, one would expect the broader signal to be at the relatively higher field ($\underline{H}$-C3-OH), say at about δ4.2; and the downfield signal at δ5.26 to be narrower and doublet like. On the basis of n.m.r. spectrum., the compound, m.p. 162° has been assigned the structure (CCXXVII).

This was further supported by the fact that the formate (CCXXVII) on mild hydrolysis, as expected provided the diol (CCXIX); though it must be pointed out that the alternate structure (CCXXVIII) would have given the same diol (CCXIX) on hydrolysis.

It is worthwhile to comment on the mode of the formation of the formate (CCXXVII) in this reaction. The epoxides(in rigid cyclic system, say cyclohexane in the chair conformation) normally open to furnish diaxially oriented functionalities. If it be assumed that the α-epoxide (CCXVIII) is involved as the precursor, then from mechanistic consideration one should get 3α-hydroxy-4β-formyloxycholest-5-en-7-one (CCXXVIII) as the product of formolysis and not 3α-formyloxy-4β-hydroxycholest-5-en-7-one (CCXXVII) as shown in the following scheme. (Although some deformation of ring A is possible because of C5-C6 double bond).

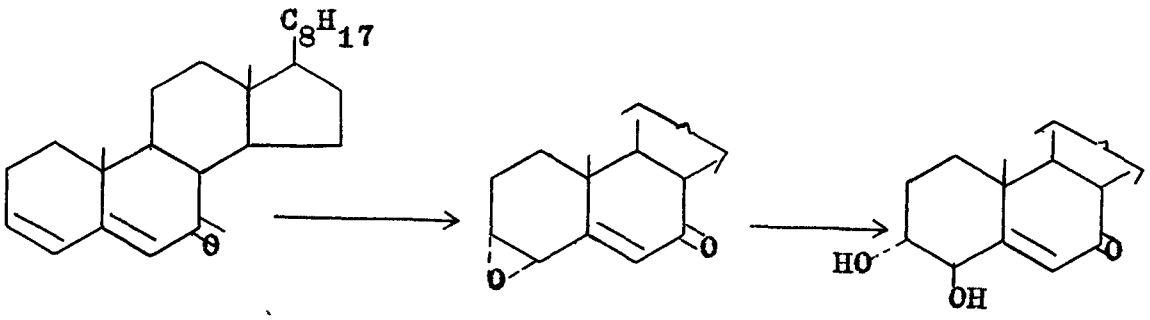


(CCXVIII)

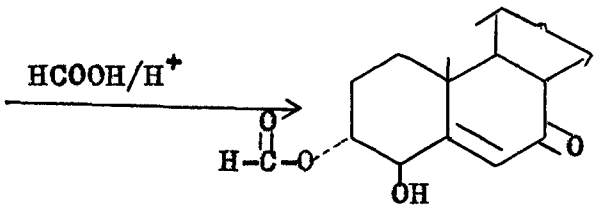


(CCXXVIII)

The epoxide (CCXVIII) does indeed open to give the diaxially oriented dihydroxy compound (CCXIX) on mild hydrolysis. However, as argued earlier, the n.m.r. values support the structure (CCXXVII). Alternatively it is reasonable to believe that the precursor of 3α-formate compound (CCXXVII) is the diol (CCXIX) which is formed during the course of the reaction and undergoes selective esterification of the C3-OH group. In the diol (CCXIX) both the C3, and C4-hydroxyl groups are axial and therefore should show reluctance to ready esterification because of 1,3-diaxial interaction. However, the axial OH at C4 (β-oriented) would be more affected because of its interaction with C10-methyl group (severe interaction), and C2-axial hydrogen and therefore, would be less accessible for esterification in comparison to C3-OH (α-oriented, axial) which would have interaction with only C1-axial hydrogen. This could account for the preferential esterification of C3-OH.

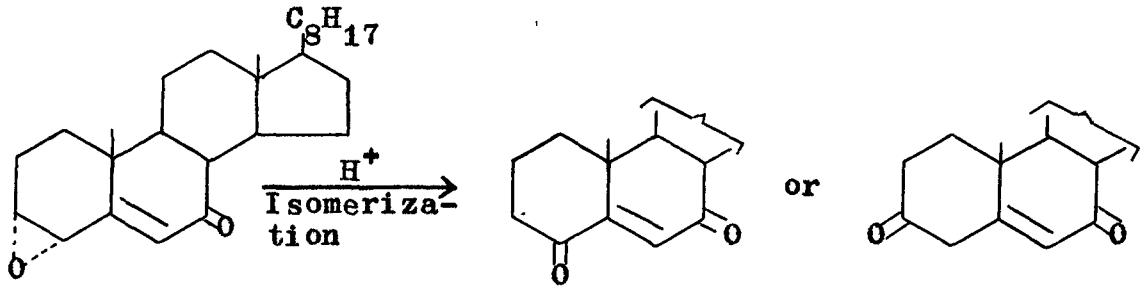


(CCXVII) (CCXVIII) (CCXIX)

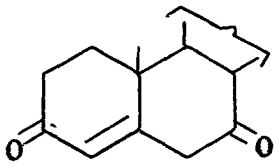


Characterization of the compound, m.p. 165° as cholest-5-ene-3,7-dione (CCXXX).

The compound, m.p. 165° analysed correctly for $C_{27}H_{42}O_2$. From the elemental composition it is apparent that only one oxygen has been incorporated during the course of the reaction. The i.r. spectrum gave peaks at 1705 (C=O), 1680 (C=C-C(=O)-) and 1625 cm^{-1} (C=C). Its u.v. spectrum showed absorption maxima at 242 nm (log ϵ 3.65) thus further supporting the presence of an α,β-unsaturated carbonyl chromophore. The n.m.r. spectrum gave signals at δ6.1s (1 proton; C6-H, vinylic proton), 2.15 umc (4 protons, C2-H_2 and C4-H_2), 1.2 (C10-Me), 0.71 (C13-Me), 0.95 and 0.85 (other methyl signals); there was no other signal in the region δ2.5-10 (except the one at δ 6.1 as mentioned above). From the elemental composition and spectral data, it is clear that this compound (m.p. 165°) is none of the expected lactones (CCXXI) and (CCXXII). The i.r. spectrum clearly showed the presence of two carbonyl functions (1705 for saturated ketone, and 1680 cm^{-1} for an α,β-unsaturated ketone). Two enediones (CCXXIX) and (CCXXX) can result from the acid-catalysed isomerization of the intermediate epoxide (CCXVIII).



(CCXVIII) (CCXXIX) (CCXXX)



(CCXXXa)

The i.r., n.m.r. and u.v. spectral values support the structure (CCXXX) i.e. the compound under discussion is cholest-5-ene-3, 7-dione (CCXXX) and not cholest-5-ene-4,7-dione (CCXXIX). It is reasonable to assume that a small amount of cholest-4-ene-3, 7-dione (CCXXXa) may also be present in equilibrium.

EXPERIMENTAL

EXPERIMENTAL

All melting points are uncorrected. Infra-red spectra were determined in KBr with a Perkin-Elmer 237 Spectrophotometer. N.m.r. spectra were run in $CDCl_3$ on a Varian A60/HA 100 instrument with TMS as the internal standard. Ultraviolet spectra were determined in 95% ethanol with an Unicam Sp 800 spectrophotometer. Mass spectra were measured in an AEI MS 9 spectrometer using a direct insertion sample inlet system. Rotations were determined in chloroform. Thin layer chromatographic plates were prepared from silica gel G and sprayed with perchloric acid (20% aqueous solution). Light petroleum refers to a fraction of b.p. 60-80°. N.m.r. values are given in ppm (s, singlet; d, doublet; t, triplet; br, broad; umc, unresolved multiplet centered at; mc, multiplet centered at). I.r. values are given in cm^{-1} (s, strong; m, medium; w, weak; br, broad).

3β,5,6β-Trihydroxy-5α-cholestane.

A mixture of cholesterol (20 g) and formic acid (20ml, 88%) was heated on a water bath at 70-80° for 5 minutes and then allowed to attain room temperature. Hydrogen peroxide (20 ml; 30%) was added to the mixture and it was kept at room temperature for 12 hours with occasional shaking. Boiling water (ca 300 ml) was added with stirring and the reaction mixture allowed to attain room temperature when a white granular solid separated which was filtered under suction and air-dried. The solid was dissolved in methanol (600 ml) and the solution heated with sodium hydroxide solution (20 ml; 25%) for 10 minutes on a

steam bath. It was acidified with hydrochloric acid and diluted with boiling water (300 ml). The triol obtained on cooling was collected by filtration under reduced pressure and recrystallized from methanol (18 g), m.p. 237-239°, (reported[148] m.p. 237-239°).

5-Hydroxy-5α-cholestane-3,6-dione (CXC).

A suspension of cholestane-3β,5α,6β-triol (5 g) in acetone (200 ml) was cooled in an ice bath. Jones' reagent (15 ml) was added gradually with stirring over a period of 30 minutes. Water (200 ml) was added to the reaction mixture and the precipitate thus obtained was collected by filtration under suction. The crude product was subjected to column chromatography (silica gel, 100 g). Elution with chloroform gave the desired compound (CXC), which was recrystallized from methanol (3.0 g), m.p. 255° (reported[139] m.p. 232-253°); $\nu_{max.}$ 3345m (OH), 1720s cm^{-1} (C=O).

Cholest-4-ene-3,6-dione (XLVII).

A mixture of 5-hydroxy-5α-cholestane-3,6-dione (CXC) (1.0 g), dioxan (70 ml), and conc. sulphuric acid (1 ml) was heated under reflux for 1 hour. The solvent was removed under reduced pressure and the residue was diluted with water and extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution (5%) and water and dried

(anhydrous sodium sulphate). Removal of the desiccant and the solvent provided the desired dione (XLVII), which was recrystallised from light petroleum (0.71 g), m.p. 122-123° (reported[137] m.p. 122-123°); λmax. 252 nm (ϵ 10,300); νmax. 1680s, 1615, 1595 cm^{-1}; δ6.16s (C4-H), 2.6 mc(C2-H_2 and C7-H_2), 1.16 (C10-Me), 0.72 (C13-Me), 0.96, 0.90, 0.84 (other methyl protons); M^+ 398 ($C_{27}H_{42}O_2$).

3β-Acetoxycholest-5-ene.

A mixture of cholesterol (100 g), pyridine (150 ml) and freshly distilled acetic anhydride (100 ml) was heated on a water bath for 2 hours. A light brown solution was obtained which, after allowing to cool to room temperature, was poured into crushed ice-water mixture with stirring. A white precipitate was obtained which was filtered under suction, washed with water and air dried. The crude acetate was recrystallized from acetone-ether mixture to give the pure product (96 g), m.p. 114-115° (reported[149] m.p. 116°).

3β-Acetoxy-6-nitrocholest-5-ene.

Cholesteryl acetate (10 g) was covered with nitric acid (d, 1.42; 250 ml) and sodium nitrite (10 g) was gradually added

over a period of 1 hour with continuous stirring. Slight external cooling was also effected during the course of the reaction and the stirring continued for additional 2 hours. A pale yellow spongy mass separated on the surface of the mixture. The mixture was diluted with cold water (200 ml) when a green coloured solution with yellow precipitate was obtained. The whole mass was extracted with ether and the ethereal solution washed with water, sodium bicarbonate solution (5%)(until the washing became pink) and water and dried over anhydrous sodium sulphate. Removal of the desiccant and the solvent provided an oil which crystallized from methanol and acetone in traces (7.1 g), m.p. 104° (reported[150] m.p. 103-104°); $\nu_{max.}$ 1740s ($CH_3\underline{COO}$-), 1515s (C=C-NO_2), 1233s cm^{-1} (acetate); M^+ 473 ($C_{29}H_{47}NO_4$).

3β-Acetoxy-5α-cholestan-6-one (CXV).

3β-Acetoxy-6-nitrocholest-5-ene (6.0 g) was dissolved in glacial acetic acid (250 ml) and zinc dust (12.0 g) added in small portions with shaking. The suspension was heated under reflux for 4 hours. Water (10 ml) was also added during the course of the reaction. The hot solution was filtered, cooled to room temperature and diluted with a large excess of water. The precipitate thus obtained was taken in ether and the ethereal solution washed with water, sodium bicarbonate solution (10%), water and dried over anhydrous sodium sulphate. Removal of the

desiccant and the solvent gave an oil which crystallized from methanol to provide the desired ketone (CXV)(4.1 g), m.p. 128-129° (reported[151] m.p. 127-128°).

3β-Acetoxy-5α-bromocholestan-6-one (CCXII).

3β-Acetoxy-5α-cholestan-6-one (CXV)(4.4 g) in acetic acid (10 ml) and ether (50 ml) was treated with a solution of bromine in acetic acid (32 ml; 5%); the addition was completed over a period of 1 hour. (The reaction was catalysed with a few drops of hydrobromic acid). Decolourisation proceeded rapidly and the crystalline material separated after the addition of approximately half of the bromine solution. The ether was removed under reduced pressure and the crystals collected and recrystallized from light petroleum from which 3β-acetoxy-5α-bromocholestan-6-one (CCXXII) (3.7 g) separated as plates, m.p. 162° (reported[73] m.p. 162°); δ5.3br (C3-H), 2.4d (J=7 Hz, C7-H_2), 2.01s (CH_3COO-), 1.0 (C10-Me), 0.7 (C13-Me), 0.91, 0.85 (other methyl protons).

3β-Acetoxycholest-4-en-6-one.

A mixture of 3β-acetoxy-5α-bromocholestan-6-one (CCXII) (1.0 g) and pyridine (10 ml) was heated under reflux for about 6 hours under anhydrous conditions. The reaction mixture was poured into ice cold water, acidified with hydrochloric acid and

extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. Removal of the desiccant and the solvent provided an oil which was crystallized from methanol to give the desired ketone (0.7 g), m.p. 108-109° (reported[73] m.p.110°); ν max. 1736s ($CH_3\underline{C}OO$-), 1680s (C=C-$\underline{C}$=O), 1238s cm^{-1} (acetate); δ6.1 (C4-$\underline{H}$), 5.35br (C3-$\underline{H}$), 2.05s ($C\underline{H}_3COO$-), 1.0 (C10-Me), 0.71 (C13-Me), 0.93—0.82 (other methyl protons); M^+ 442 ($C_{29}H_{46}O_3$).

5α-Cholestane-3,6-dione (CLXXXIX).

A mixture of 3β-acetoxycholest-4-en-6-one (1.0 g) and conc. hydrochloric acid (1 ml) and ethanol (25 ml) was heated under reflux for 1 hour. Half of the alcohol was removed under reduced pressure when the dione (CLXXXIX) started crystallizing out. The solid was filtered under suction and recrystallized from ethanol (0.75 g), m.p. 166° (reported[73] m.p. 169°); ν max. 1710s cm^{-1} (CO); δ 2.1-2.7 (7 protons, C2-$\underline{H}_2$, C4-$\underline{H}_2$, C5-$\underline{H}$, C7-$\underline{H}_2$), 0.9 (C10-Me), 0.7 (C13-Me), 0.85, 0.8 (other methyl signals); M^+ 400 ($C_{27}H_{44}O_2$). This compound was identical with a sample of the diketone (CLXXXIX) prepared according to Heilbron[73] et al. by the base catalysed hydrolysis of 3β-acetoxycholest-4-en-6-one.

3,3,6,6-Bis-ethylenedioxy-5α-cholestane (CXCI).

A mixture of 5α-cholestane-3,6-dione (CLXXXIX) (5 g), ethylene glycol (50 ml; azeotropically dried), sodium dried benzene (400 ml) and p-toluenesulphonic acid monohydrate (ca 100 mg) was heated in a Dean and Stark apparatus for 20 hours. After allowing the reaction mixture to attain room temperature, it was treated with $NaHCO_3$ solution (10%) and extracted with ether. The solvent layer was washed with water and dried (anhydrous Na_2SO_4). The organic solvents were distilled off under reduced pressure to give an oily residue which crystallized from light petroleum-ether to give the bis-acetal (CXCI)(3.5 g), m.p. 120° (homogeneous by t.l.c., solvent system,pet. ether:ether), M^+ 488 ($C_{31}H_{52}O_4$); ν_{max}. 1145(m), 1105(m), 1039(s), and 1035 cm^{-1}; δ 3.86 mc (8 protons, C3-OCH_2-CH_2O-,C6-OCH_2-CH_2O-).

Analysis. Found: C, 75.8; H, 10.5.

$C_{31}H_{52}O_4$ requires : C, 76.23; H, 10.65%.

Reaction of (CXCI) with aqueous HCl: 5α-cholestane-3,6-dione (CLXXXIX).

A solution of 3,3,6,6-bis-ethylenedioxy-5α-cholestane (CXCI) (350 mg) in acetone (40 ml) containing conc. HCl (A.R.) (2 ml) and water (1.0 ml) was heated under reflux for one hour. The reaction mixture was then poured into water and then extracted

with ether. The ethereal solution was washed with water, $NaHCO_3$(5%) and water and dried (Na_2SO_4). Evaporation of the ether left an oily residue which crystallized from ethanol to give (CLXXXIX)(220 mg), m.p. 168°. Mixed m.p. determination with an authentic sample showed no depression[73].

5-Hydroxy-3,3,6,6-bis-ethylenedioxy-5α-cholestane (CXCIII).

A mixture of 5-hydroxy-5α-cholestane-3,6-dione (CXC) (3 g), ethylene glycol (30 ml; azeotropically dried), sodium-dried benzene (200 ml) and p-toluenesulphonic acid monohydrate (ca 100 mg) was heated in a Dean and Stark apparatus for 22 hours. After allowing the reaction mixture to attain room temperature, it was treated with $NaHCO_3$ solution (10%) and extracted with ether. Removal of the solvent under reduced pressure gave an oil (2.9 g) which was shown to be a mixture of three compounds (t.l.c. solvent system pet. ether-ether) and subjected to column chromatography over silica gel (60 g). The column was eluted in 20 ml portions with petroleum-ether (1-10), pet. ether-ether (15:1)(fractions 11-15), pet. ether:ether (10:1) (fractions 16-20), pet.-ether-ether (5:1) (fraction 21-30). Fractions 1-10 did not give any product. Fractions 11-14 (identical by t.l.c.) were combined together to give 3,3,6,6-bis-ethylenedioxycholest-4-ene (CXCII) (0.3 g) as a crystallined solid (homogeneous by t.l.c.), m.p. 136°, M^+ 486 ($C_{31}H_{50}O_4$); $\nu_{max.}^{1640\ (C=C)}$ 1170m, 1134w, 1073w, 1034s cm^{-1} (C-O-);

δ3.85 mc (8 protons, C3-O$\underline{CH_2}\underline{CH_2}$O-; C6-O$\underline{CH_2}\underline{CH_2}$O-), δ5.83 (vinylic proton).

Analysis. Found: C, 76.3; H, 10.2.

$C_{31}H_{50}O_4$ requires : C, 76.5; H, 10.3%.

Fractions 16-18 gave cholest-4-en-3,6-dione (XLVII) (0.5 g) as solid which was crystallized from light petroleum, m.p. 123° (lit.[137] m.p. 122-123°). MS: m/e 398 (M^+, $C_{27}H_{42}O_2$); λmax. 252 nm, νmax. 1680s (C=C-C=O), 1615 and 1595 cm^{-1} (C=C-C=O); δ 6.16 (s, C4-$\underline{H}$), 2.0-2.4 (4H, C2-$\underline{H_2}$ and C7-$\underline{H_2}$), 1.1 (C10-Me), 0.70 (C13-Me 0.92, 0.90, 0.83 (other methyl signals).

Fractions 22-27 gave 5-hydroxy-3,3,6,6-bisethylenedioxy-5α-cholestane (CXCIII) (1.0 g) as solid which was crystallized from light petroleum, m.p. 124°; νmax. 3550 (OH group), 1180 m, 1125s, 1086m, 1052s cm^{-1} (C-O-); δ3.93 mc (8 protons; C3-O$\underline{CH_2}\underline{CH_2}$-O; C6-O$\underline{CH_2}\underline{CH_2}$O-), 1.06 (C10-Me), 0.7 (C13-Me), 0.8 and 0.9 (methyl protons).

3,3,6,6-Bisethylenedioxycholest-4-ene (CXCII).

A mixture of ethylene glycol (40 ml) and sodium-dried benzene (300 ml) was heated in a Dean and Stark apparatus for 4 hours to remove the traces of water. Cholest-4-ene-3,6-dione (XLVII) (4.0 g) and p-toluenesulphonic acid monohydrate (ca 100 mg) were added and the mixture was heated under reflux for 16 hours

with simultaneous removal of water. Saturated $NaHCO_3$ solution was then added to the reaction mixture. once it attained the room temperature and the benzene layer was separated. The organic layer was washed with water and dried (anhydrous Na_2SO_4). Removal of the solvent under reduced pressure left an oily residue which crystallized from light petroleum ether to give the bis-acetal (CXCII)(3.1 g), m.p. 136° (homogeneous by t.l.c., solvent system, pet.ether:ether). M^+ 486 ($C_{31}H_{50}O_4$); $\nu_{max.}^{1640\ (C=C)}$ 1170m, 1134w, 1073w, 1034s (C-O-); δ 3.85 mc (8 protons, C3-O$\underline{CH_2}\underline{CH_2}$O-; C6-O$\underline{CH_2}\underline{CH_2}$O-), 5.83s (vinylic proton).

Analysis. Found: C, 76.2; H, 10.4.

$C_{31}H_{50}O_4$ requires : C, 76.5; H, 10.3%.

<u>$LiAlH_4$-$AlCl_3$ Reduction of 3,3,6,6-bis-ethylenedioxy-5α-cholestane (CXCI): 3β,6β-(2',2"-bis-hydroxyethoxy)-5α-cholestane (CXCIV).</u>

To a well stirred mixture of $LiAlH_4$ (2.0 g) and $AlCl_3$ (7.0 g) in sodium-dried ether (200 ml) was added an ethereal solution of the bis-acetal (CXCI) (4.0 g) dropwise over a period of 20 minutes. After the addition was complete the reaction mixture was kept at its reflux temperature for 4 hours. A cold mixture of ethyl acetate and moist ether was then added to destroy the excess of the reducing agent and aluminium complexes

were decomposed by careful addition of cold, dil. H_2SO_4 (100 ml). The ethereal layer was separated and washed successively with dilute H_2SO_4, $NaHCO_3$ solution (5%) and water and dried (anhydrous sodium sulphate). The oily residue (5 g), obtained on evaporation of the ether, was subjected to column chromatography over silica gel (100 g, NCL). The column was eluted in 50 ml portions with pet.ether (fractions 1-10), pet.ether-ether (10:1) (fractions 11-15), pet.ether-ether (8:1) (fractions 16-20); pet.ether-ether (4:1) (fractions 21-25), pet.ether-ether (2:1) (fractions 26-32), pet.ether-ether (1:1) (fractions 33-35), ether (fractions 36-40). Fractions 27-30 gave the bis-hydroxyether (CXCIV) as an oil which was solidified on standing (2.1 g), m.p. 174°; $\nu_{max.}$ 3450br (OH), 1100, 1040 and 1020 cm^{-1} (C-O-); δ 3.66 mc (C3-O-CH_2-CH_2-O- and C6-O-CH_2-CH_2-O-), δ 3.3 (C3H and C6-H), 1.03 (C10-CH_3), 0.70(C13-CH_3) 0.81, 0.91(other methyl protons).

Analysis. Found: C, 75.3; H, 11.1.

$C_{31}H_{56}O_4$ requires : C, 75.6; H, 11.3%.

3β,6β-(2',2"-Bis-acetoxyethoxy)-5α-cholestane (CXCV).

A mixture of the bishydroxyether (CXCIV) (0.5 g), pyridine (2 ml, freshly distilled over KOH) and acetic anhydride (2 ml) was allowed to stand at room temperature for 24 hours and then warmed on a water bath for 1 hour. Usual work up of the reaction

mixture gave an oil (0.52 g) which was purified by column chromatography over silica gel (15 g, NCL). The column was eluted in 25 ml portions with pet.ether (fractions 1-5), pet.ether-ether (10:1) (fractions 6-8), pet.ether-ether (5:1) (fractions 9-12), pet.ether-ether (2:1) (fractions 13-15), ether (fractions 15-20). Fractions 1-8 did not give any product. Fractions 9-11 (identical by t.l.c. were combined together to give (CXCV) (0.22 g) which was recrystallized from pet.ether, m.p. 143°; νmax. 1735, 1240 (CH_3COO), 1100, 1040 and 1020 cm^{-1}(C-O-); δ4.16 (dist.t, 4 protons, C3-O-CH_2-$\underline{CH}_2$-OAc; C6-O-CH_2-$\underline{CH}_2$-OAc), 3.6 (t, 4 protons, C3-O-$\underline{CH}_2$-CH_2-OAc; C6-O-$\underline{CH}_2$-CH_2OAc), 3.28 (mc, 2 protons, C3-$\underline{H}$ and C6-$\underline{H}$), 2.1s (6 protons, C3-O-CH_2-CH_2-O-$\overset{O}{\overset{\|}{C}}$-$\underline{CH}_3$; C6-O-$CH_2$-$CH_2$-$\overset{O}{\overset{\|}{C}}$-$\underline{CH}_3$), 1.03 (C10-$CH_3$), 0.70 (C13-Me), 0.8, 0.91(other methyl protons).

Analysis. Found: C, 73.1; H, 10.2.

$C_{35}H_{60}O_6$ requires: C, 72.9; H, 10.4%.

Reaction of the bis-acetate (CXCV) with BF_3-etherate-Ac_2O: 3β-Acetoxy-6β-(2'-acetoxyethoxy)-5α-cholestane (CLXXVII).

A solution of the bis-acetate (CXCV) (500 mg) in sodium dried ether (5 ml) and acetic anhydride (10 ml) was cooled to 0-5° and to the cold solution was added freshly distilled BF_3 etherate (2.0 ml) which had also been cooled previously to 0-5°.

The reaction mixture was kept at 0-5° for 60 hours and then worked up in the usual manner. Evaporation of the solvent left an oily material which was crystallized from methanol-ether mixture to give 3β-acetoxy-6β-(2'-acetoxyethoxy)-5α-cholestane (CLXXVII)[62] as needles (330 mg), m.p. and m.m.p. 76-77°; $[\alpha]_D^{17}$ - 40.5°; $\nu_{max.}$ 1738, 1240 (ester carbonyl); 1117, 1050, 1026 cm^{-1} (C-O); δ4.7 br (C3-H, axial); 3.3m ($AcOCH_2CH_2O$-C6-H), 3.58 distorted t. (-O-CH_2-CH_2-OAc), 4.12 distorted t. (-O-CH_2-CH_2-OAc), 2.05s (CH_3COO-); 2.0 s (CH_3COO-), 0.96 (C10-Me), 0.68 (C13-Me), 0.90, 0.80 (other methyl groups).

Analysis. Found: C, 74.1; H, 10.7.

$C_{35}H_{56}O_5$ requires: C, 74.4; H, 10.6%.

<u>$LiAlH_4$-$AlCl_3$ Reduction of 3,3,6,6-bisethylenedioxycholest-4-ene (CXCII)</u>.

To a stirred slurry of $LiAlH_4$ (2.0 g) and $AlCl_3$ (7.0 g) in sodium dried ether (200 ml) was added dropwise an ethereal solution of the bis-acetal (CXCII) (4.0 g) over a period of 15 minutes. After the addition was complete, the reaction mixture was kept at its reflux temperature for 6 hours. It was then treated with a cold mixture of ethyl acetate and moist ether to decompose excess of the reducing agent. Cold, dilute H_2SO_4 was added cautiously with continued stirring and ethereal layer was

washed successively with dilute H_2SO_4, $NaHCO_3$ solution (5%) and water and dried (anhydrous Na_2SO_4). Removal of the solvent furnished an oily residue (3.8 g) which was found by t.l.c. (solvent system pet.ether-ether, 4:1) to be a mixture of three components. The components were separated by column chromatography over silica gel (80 g, NCL). The column was eluted in 20 ml portions with pet.ether (fractions 1-6), pet.ether-ether (10:1) (fractions 7-11), pet.ether-ether (4:1) (fractions 12-18), pet. ether-ether (2:1) (fractions 19-21), pet.ether-ether (1:1) (fractions 22-28), ether (fractions 29-37), ether-methanol (10:1) (fractions 38-42). Fractions 1 and 2 were combined together to give a compound, m.p. 62°, (75 mg) which was suspected to be the mixture of 5α- and 5β-cholestane (CCI). I.R. spectrum was devoid of any significant peak. N.m.r. spectrum was featureless (δ1.8-10), δ1.2, 0.91, 0.83 (methyl signals).

Analysis. Found: C, 87.4; H, 12.6.
$C_{27}H_{48}$ requires : C, 87.09; H, 12.9%.

Fractions 7-25 did not give any product. Fractions 26-29 (identical by t.l.c.) were combined together to give 3β-(2'-hydroxyethoxy)-5α-cholestan-6-one (CCIV), (0.82 g), m.p. 109° (homogeneous by t.l.c.), $\nu_{max.}$ 3550 (OH), 1710 (C=O), 1098, 1062 and 1040 cm^{-1} (C-O-). δ 3.7 mc (4 protons; C3-O-$\underline{CH}_2$-$\underline{CH}_2$-O-), 3.1br (1 proton, C3-$\underline{H}$), 2.25mc (2 protons; $\underset{\underset{O}{\|}}{C}$-$\underline{CH}_2$).

Analysis. Found: C, 77.8; H, 11.1.
$C_{29}H_{50}O_3$ requires: C, 78.0; H, 11.2%.

Fractions 32-35 provided 3β,6β-bishydroxyethoxy-cholest-4-ene (CCII) crystallized from pet.ether-ether mixture (0.92 g), m.p. 126°, ν_{max}. 3450br (OH), 1650 (C=C), 1098, 1067 and 1040 cm^{-1} (C-O-); δ 5.9 (d like, C4-H), 3.73 mc (C3-O-CH_2-CH_2-O-; C6-O-CH_2-CH_2-O-; C3-H and C6-H), 1.05 (C10-Me), 0.9 (C13-CH_3), 0.8, 0.9 (other methyl signals).(Found: C, 75.62; H, 11.0. $C_{31}H_{54}O_4$ requires C, 75.91; H, 11.02%).

3β-(2'-Acetoxyethoxy)-5α-cholestan-6-one (CCV).

A mixture of the hydroxyether (CCIV) (0.5 g), pyridine (2 ml, freshly distilled over KOH) and acetic anhydride (2 ml) was allowed to stand at room temperature for 24 hours and then warmed on a water bath for 1 hour. Usual work up procedure gave the acetate (CCV) as a noncrystallizable oil (0.4 g) which was purified by column chromatography. ν_{max}. 1736, 1235 (CH_3-$\overset{O}{\overset{\|}{C}}$-O-), 1710 cm^{-1} (C=O); δ 4.1t (C3-O-CH_2-CH_2-OAc), 3.70t (2 protons, C3-O-CH_2-CH_2-OAc), 3.1br (1 proton, $W_{\frac{1}{2}}$ 16 Hz, C3- H, α, axial), 2.3 mc (2 protons, CH_2-$\overset{O}{\overset{\|}{C}}$-), and 2.0s (3 protons, -O-$\overset{O}{\overset{\|}{C}}$-$CH_3$).

Analysis. Found: C, 76.4; H, 10.4.

$C_{31}H_{52}O_4$ requires: C, 76.2; H, 10.7%.

Reaction of the acetate (CCV) with BF_3-etherate-Ac_2O: 3β-Acetoxy-5α-cholestan-6-one (CXV).

A mixture of the acetate (CCV) (100 mg) in dry ether

(4.0 ml), acetic anhydride (5 ml) and freshly distilled BF_3 etherate (1.0 ml) was allowed to stand at 0-5° for 60 hours. The reaction mixture was then poured into ice-cold water, and after a few hours, extracted with ether. The ether extract was washed with $NaHCO_3$ solution (10%) and water and dried (anhydrous Na_2SO_4). Evaporation of the solvent gave 3β-acetoxy-5α-cholestan-6-one (CXV) (identical by t.l.c. with an authentic sample)., m.p. and mixed m.p. 128°.

α-Bromination of 3β-acetoxy-5α-cholestan-6-one (CXV): 3β-Acetoxy-5,7,7-tribromo-5α-cholestan-6-one (CCIX).

To a solution of (CXV) (5.5 g) in acetic acid (12 ml) and ether (75 ml) with a few drops of HBr was added a solution of bromine in acetic acid (5 ml of bromine in 50 ml of acetic acid) at room temperature over a period of 75 minutes. The mixture was then heated under reflux for 2 hours, ether removed by distillation and the solution set aside in the cold for 24 hours. Water (5 ml) was added to the reaction mixture followed by extraction with ether. The ethereal extract was washed successively with water, sodium bicarbonate solution (5%) and water and dried (Na_2SO_4). Removal of the solvent gave a non-crystallizable oil (~5 g) which was subjected to column chromatography over silica gel (NCL grade, 100 g). Fractions of 20 ml were collected. Eluates from pet. ether-ether (10:1) gave the unreacted ketone (CXV)(~60 mg), m.p. and

m.m.p. 128-129°. Eluates from the same solvent system (9:1) gave 3β-acetoxy-5,7,7-tribromo-5α-cholestan-6-one (CCIX) (homogeneous by t.l.c.) crystallized from pet. ether (1.3 g), m.p. 186°; positive Beilstein test; $[\alpha]_D^{25}$ - 89° (Found: C, 51.4; H, 6.7. $C_{29}H_{45}O_3Br_3$ requires C, 51.1; H, 6.6%); νmax. 1739s, 1221s (acetate), 1720s (C=O), 750 cm^{-1} (C-Br)[143]; δ 5.4 (m, C3-H, axial, α-oriented, 7 peaks, J = 10 and 5 Hz)[141], 2.05 (s, CH_3COO-), 1.05 (C10-Me), 0.78 (C13-Me), 0.98, 0.92, 0.85 (other methyl protons).

In one or two experiments under the conditions described above the acetoxy ketone (CXV) (5 g) provided 3β-acetoxy-5,7β-dibromo-5α-cholestan-6-one (XLV), crystallized from pet. ether (1.4 g), m.p. 140°; positive Beilstein test; $[\alpha]_D^{25}$ - 9° (Found: C, 57.95; H, 7.6. $C_{29}H_{46}O_3Br_2$ requires C, 57.8; H, 7.64%); νmax. 1732s, 1250s (acetate), 1710s (C=O), 750m cm^{-1} (C-Br)[143]; δ 5.37 (d, J = 9.5 Hz, C7-H, axial, α-oriented), 5.25 (br, C3-H, axial, α-oriented)[141], 2.04 (s, CH_3COO-), 0.98 (C10-Me), 0.70 (C13-Me), 0.95, 0.90, 0.83 (other methyl signals).

Dehydrobromination of 3β-acetoxy-5,7,7-tribromo-5α-cholestan-6-one (CCIX).

The tribromide (CCIX) (1.0 g) in freshly distilled pyridine was heated under reflux for 8 hours. The colour of the reaction mixture became dark red during the course of reaction. The

reaction mixture was extracted with ether and ethereal solution washed successively with water, dilute sulphuric acid, water, sodium bicarbonate solution (5%) and water and dried (Na_2SO_4). Removal of the solvent gave an oil (~1 g) which was chromatographed over silica gel (20 g). Fractions of 10 ml were collected. Eluates from pet.ether-ether (15:1) gave 3-acetoxycholesta-2, 4-dien-6-one (XLVI), crystallized from pet.ether (270 mg), m.p. 140° (lit.[76] m.p. 139-140°)(Found: C, 79.2; H, 9.8. $C_{29}H_{44}O_3$ requires C, 79.09; H, 10.0%); λ max. 317 nm; νmax. 1755s (acetate carbonyl), 1675s (C=C-C=O), 1645m, 1570m (C=C), 1250s cm^{-1}(acetate); δ6.57 (d, J = 1.5 Hz, C4-H; long range coupling with C2-H, M pattern), 5.67 (t, each splits into doublet, J = 1.5 Hz, C2-H), 2.4 (d like, $COCH_2$-C8-H), 2.05 (s, CH_3COO-), 1.1 (C10-Me), 0.70 (C13-Me), 0.92,0.9 0.83 (other methyl signals); MS: m/e 440 (M^+, $C_{29}H_{44}O_3$), 425 (M^+-Me), 398 (M^+-CH_2CO)[145], 383 (398-15) and lower mass peaks.

Further elution with the same solvent system (10:1) gave cholest-4-ene-3,6-dione (XLVII) crystallized from pet.ether (130mg), m.p. 123° (lit.[76,137] m.p. 122-123°) (Found: C, 81.2; H, 10.3. $C_{27}H_{42}O_2$ requires C, 81.4; H, 10.55%); MS: m/e 398 (M^+, $C_{27}H_{42}O_2$); λmax. 252 nm; νmax. 1680s (C=C-C=O), 1615 and 1595 cm^{-1}(C=C-C=O); δ6.16 (s, C4-H), 2.0-2.4 (4H, C2-H_2 and C7-H_2), 1.1 (C10-Me), 0.70 (C13-Me), 0.92, 0.90, 0.83 (other methyl signals). An authentic sample of (XLVII) was prepared according to literature method[137] and no depression in mixed m.p. was observed.

Dehydrobromination of 3β-acetoxy-5,7β-dibromo-5α-cholestan-6-one (XLV).

The dehydrobromination of (XLV) (300 mg) was carried out in the manner described for (CCIX). After usual work up of the reaction mixture, (XLVI) and (XLVII) were obtained (90 and 40 mg, respectively), comparable with the previously obtained samples in all respects.

Acid hydrolysis of (XLVI).

The compound (XLVI) (200 mg) in dioxan (20 ml) with a few drops of conc. sulphuric acid was heated under reflux for 1 hour. The solvent was removed under reduced pressure and the residue extracted with ether. After usual work up of the ether extract, (XLVII) was obtained which crystallized from pet.ether (∿170 mg), m.p. and m.m.p. 122-123°.

Attempted preparation of 3β-acetoxy-7α-bromocholestan-6-one(CCVII): 1-Methylcholesta-1,3,5(10)-trien-6-one (CCXIV).

A solution containing 2.5 g of bromine dissolved in 25 ml of acetic acid was added dropwise to a solution of 5.8 g of 3β-acetoxycholestan-6-one (CXV) in 80 ml of ether and 15 ml of acetic acid and the resulting solution was maintained at reflux temperature for 22 hours. A few drops of HBr were also added to catalyse

the reaction. The ether was removed under reduced pressure and the acetic acid solution was diluted with water to turbidity and was extracted with ether. The ethereal solution was washed successively with water, sodium bicarbonate solution (5%), water and dried (anhydrous sodium sulphate). Removal of the solvent at reduced pressure gave an oil (5 g) which was chromatographed over silica gel (100 g). Fractions of 20 ml were collected. Eluates from pet.ether-ether (15:1) gave 1-methylcholesta-1,3,5(10)-trien-6-one (CCXIV), crystallized from pet.ether (0.8 g), m.p.140°. λmax. 255, 335 nm; νmax. 1680 cm^{-1} (conjugated ketonic group); δ 2.4s (methyl protons at C1), 7.26 mc (C2-$\underline{H}$, C3-$\underline{H}$), 7.9d,d (J=8 Hz, 3 Hz, C4-$\underline{H}$).

Analysis. Found: C, 84.9; H, 10.2.

$C_{27}H_{40}O$ requires : C, 85.2; H, 10.5%.

Further elution with the same solvent system (9:1) gave 3β-acetoxy-5α-bromocholestan-6-one (CCXII), m.p. 161° (lit.[73] m.p. 162°); δ 5.3br (C3-H), 2.4d (J=7 Hz, C7-$\underline{H}_2$), 2.01s ($C\underline{H}_3COO$-), 1.0 (C10-Me), 0.7 (C13-Me), 0.91, 0.85 (other methyl protons).

Further elution in the same solvent system (4:1) gave 5α-cholestane-3,6-dione (CLXXXIX), m.p. 168° (lit.[73] m.p. 169°); νmax. 1710 cm^{-1} (CO); δ 2.1-2.7 (7 protons, C2-$\underline{H}_2$, C4-$\underline{H}_2$, C5-$\underline{H}$, C7-$\underline{H}_2$), 0.9 (C10-Me), 0.7 (C13-Me), 0.85, 0.80 (other methyl signals).

Chromic acid oxidation of 3β-acetoxycholest-5-ene: 3β-Acetoxycholest-5-en-7-one (CLXIII).

To a stirred solution of 3β-acetoxycholest-5-ene (54 g) in glacial acetic acid (600 ml), a solution of chromium trioxide (35 g) in acetic acid (100 ml; 50%) was added over a period of 2 hours, maintaining the temperature around 55-60° throughout. After complete addition, the solution was stirred for an additional period of 2 hours at the same temperature. The excess of chromic acid was destroyed by the addition of methanol (30 ml) and then acetic acid (400 ml) was removed by distillation under reduced pressure. The remaining liquid was diluted with water (25 ml) and allowed to stand in the cold for 12 hours. The crystalline 3β-acetoxycholest-5-en-7-one (CLXIII) which separated out, was removed by filtration under suction and washed with cold acetic acid (30 ml; 80%). Several recrystallisations from light petroleum gave 3β-acetoxycholest-5-en-7-one (CLXIII), m.p. 161-163° (reported[152] m.p. 164°); M^+ 442 ($C_{29}H_{46}O_3$); $\nu_{max.}$ 1730 s (CH_3-CO-O), 1668s (C=C-CO), 1235s cm^{-1} (acetate).

Cholesta-3,5-dien-7-one (CCXVII).

To a solution of 3β-acetoxycholest-5-en-7-one (CLXIII) (5.0 g) in absolute ethanol (100 ml) was added hydrochloric acid (5 ml; 12N) and the reaction mixture was heated under reflux for

2 hours. On allowing the reaction mixture to cool, the dienone (CCXVII) separated as plates which was filtered and recrystallized from ethanol (3.5 g), m.p. 116° (reported[153] m.p. 118°); M^+ 382 ($C_{27}H_{42}O$); $\nu_{max.}$ 3030w (C=C), 1665s, 1625s, 1600m cm^{-1} (C=C-C=C-C=O).

Reaction of cholesta-3,5-dien-7-one (CCXVII) with perbenzoic acid: 3α,4α-Epoxycholest-5-en-7-one (CCXVIII) and 3α,4β-dihydroxycholest-5-en-7-one (CCXIX).

To a solution of cholesta-3,5-dien-7-one (CCXVII) (5.0 g) in chloroform (25 ml), a chloroform solution of perbenzoic acid (2.5 mole equivalent) and a few crystals of p-toluenesulphonic acid were added and the reaction mixture was kept in the dark for 24 hours. The solvent was removed by distillation under reduced pressure, and the residue was diluted with water, extracted with ether and the ethereal layer was washed with water, sodium bicarbonate solution (10%), water and dried (anhydrous sodium sulphate). Removal of the solvent gave an oil (3.0 g) which was chromatographed over silica gel (60 g) (each fraction of 20 ml was taken). Elution with light petroleum, light petroleum-ether (4:1) (fractions 1-8) gave no organic substance. Elution with light petroleum-ether (2:1) (fractions 10-16) gave a solid which was crystallized from light petroleum to give 3α,4α-epoxycholest-5-en-7-one (CCXVIII), m.p. 136°;

M^+ 398 ($C_{27}H_{42}O_2$); (Found: C, 81.8; H, 10.2. $C_{27}H_{42}O_2$ requires: C, 81.4; H, 10.5%); λmax. 241 nm (log ϵ 3.46); νmax. 1680 (C=C-C=O), 1638 (C=C), 870 and 775 cm^{-1} (epoxide ring); δ (100 MHz) 5.95s (C6-$\underline{H}$), 3.38m (C3β-$\underline{H}$ and C4β-$\underline{H}$; $W_{\frac{1}{2}}$ = 5.0 Hz), 1.08 (C19-$\underline{H}$), 0.7 (C18-$\underline{H}$), 0.82, 0.9 and 0.93 (other methyl protons).

Further elution with ether (fractions 21-25) gave another solid (homogeneous by t.l.c.) which was recrystallized from ether and light petroleum mixture to give 3α,4β-dihydroxycholest-5-en-7-one (CCXIX) (250 mg), m.p. 205°; M^+ 416 ($C_{27}H_{44}O_3$); (found: C, 78.02; H, 10.3. $C_{27}H_{44}O_3$ requires: C, 77.8; H, 10.5%); λmax. 244 nm (log ϵ 3.36); νmax. 3360 (-OH), 1680 (C=C-C=O), 1640sh (C=C), 1075, 1022 and 1015 cm^{-1} (C-O); δ (100 MHz): 5.75 (C6-$\underline{H}$), 4.05 (C3-$\underline{H}$ and C4-$\underline{H}$; $W_{\frac{1}{2}}$ = 6 Hz)[141], 1.34 (C19-$\underline{H}$), 0.62 (C18-$\underline{H}$), 0.83, 0.9 and 0.94 (other methyl protons).

Conversion of the epoxy ketone (CCXVIII) to the dihydroxy ketone (CCXIX).

A mixture of the epoxy ketone (100 mg)(CCXVIII), ethanol (20 ml), hydrochloric acid (3 ml) and water (2 ml) was heated under reflux for 30 minutes. The reaction mixture was then poured into cold water and extracted with large excess of ether, Usual work up of the reaction mixture gave a solid which was recrystallized from ether-light petroleum to give the dihydroxy ketone (CCXIX) (85 mg), m.p. and m.m.p. 204°.

3α,4β-Diacetoxycholest-5-en-7-one (CCXX).

A mixture of the dihydroxyketone (CCXIX) (400 mg), pyridine (20 ml) and acetic anhydride (8 ml) was heated on a water bath for 2 hours. The reaction mixture was then poured into cold water, extracted with ether and the ethereal solution was washed with dilute hydrochloric acid, sodium bicarbonate solution (5%) and water and dried (anhydrous sodium sulphate). Removal of the solvent gave a solid which was recrystallized from light petroleum-ether to give the diacetoxyketone (CCXX) (150 mg), m.p. 102°; M^+ 500 ($C_{31}H_{48}O_5$); (Found: C, 74.8; H, 9.4. $C_{31}H_{48}O_5$ requires: C, 74.4; H, 9.6%); λ max. 241 nm (log ϵ 3.63); νmax. 1755, 1740 (ester carbonyls), 1680 (C=C-C=O), 1640 (C=C) and 1235 cm^{-1} (Acetate); δ (100 MHz) 5.9 (C6-H), 5.22d (C4α-H, J = 3 Hz; equatorial)[141], 4.96m (C3β-H, $W\frac{1}{2}$ = 6 Hz; equatorial)[141], 2.05, 2.02 (two acetates), 1.31 ($C10-CH_3$), 0.68 ($C13-CH_3$), 0.83, 0.9 and 0.94 (other methyl protons).

Cholestane-3β,6α-diol (CCXXIII).

3β-Hydroxycholestan-6-one[154] (1.5 g) was dissolved in absolute ethanol (85 ml) and sodium metal (8.5 g) was added in small portions over a period of 2 hours with stirring. During the course of reduction, the colour of the reaction mixture changed to bright yellow. When all the sodium was dissolved,

the reaction mixture was cooled to room temperature and then diluted with excess of water, acidified with hydrochloric acid and extracted with ether. Usual work up of the ethereal solution gave a solid which was crystallized from ether to give the diol (CCXXIII)(900 mg), m.p. 217° (reported[154] m.p. 216-217°); M^+ 404 ($C_{27}H_{48}O_2$); ν max. 3350 (br;s) cm^{-1} (-OH); δ(100 MHz): 3.3br (2 protons; C3α-H and C6β-H), 0.92 (C10-CH_3) 0.64 (C13-CH_3), 0.9, 0.82 and 0.80 (other methyl protons).

Cholestane-3β,6α-diol diacetate (CCXXV).

Cholestane-3β,6α-diol (CCXXIII) (600 mg) was dissolved in dry pyridine (4 ml) and acetic anhydride (3 ml) was added. The reaction mixture was allowed to stand overnight at room temperature and then poured in ice-cooled water. The organic substance was extracted with ether and the ethereal layer was washed with dilute hydrochloric acid, sodium bicarbonate solution (10%) and water and dried (anhydrous sodium sulphate). Removal of the solvent provided an oil which was crystallized from methanol to give the diacetate (CCXXV) (440 mg), m.p. 155-56° (reported[55] m.p. 155-56°); M^+ not observed, highest mass ion peak at m/e 428 (M-CH_3COOH) was observed; νmax. 1732s (CH_3-COO), 1250s, 1235 cm^{-1}(sh) (acetate); δ (100 MHz): 4.64br (2 protons; C3α-H and C6β-H), 2.0 (6 protons; two acetate methyl groups), 1.24 (C10-CH_3), 0.64 (C13-H), 0.9, 0.82 (other methyl protons).

Cholestane-3β,6β-diol (CCXXIV).

3β-Acetoxy-5α-cholestan-6-one (CXV) (500 mg) was dissolved in absolute ethanol (70 ml) and after mixing with platinum catalyst (200 mg), hydrogen gas was passed under 20 lbs pressure for 5 hours. The catalyst was removed by filtration and the filtrate was diluted with water. Organic substance was extracted with ether and ethereal layer was washed with water and dried (anhydrous sodium sulphate). Removal of the solvent gave a solid which was crystallized from ethanol to give the diol (CCXXIV) (230 mg), m.p. 187° (reported[156] m.p. 188-189°); M^+ 404 ($C_{27}H_{48}O_2$); ν max. 3460, 3410 cm^{-1}(s)(-OH); δ(100 MHz): 3.66br (C3α-H; $W_{\frac{1}{2}}$ = 22 Hz; axial proton)[141], 3.76m (C6α-H; $W_{\frac{1}{2}}$ = 8 Hz; equatorial proton)[141], 1.02 (C10-CH_3), 0.69 (C13-CH_3), 0.82, 0.79 and 0.72 (other methyl protons).

Cholestane-3β,6β-diol diacetate (CCXXVI).

Cholestane-3β,6β-diol (CCXXIV)(200 mg) was dissolved in dry pyridine (4 ml) and acetic anhydride (2 ml) was added. The reaction mixture was allowed to stand overnight at room temperature and then poured into ice cold water. Usual work up of the reaction mixture gave the diacetate (CCXXVI) which was crystallized from ethanol (140 mg), m.p. 135° (reported[156] m.p. 136-137°); M^+ not observed, highest mass ion peak at m/e 428

(M-CH_3COOH) was observed; ν max. 1740s (CH_3COO), 1235s cm^{-1} (acetate), δ(100 MHz) 4.7br (C3α-H; $W_{\frac{1}{2}}$ = 22 Hz; axial proton)[141], 4.9m (C6α-H; $W_{\frac{1}{2}}$ = 8 Hz; equatorial proton)[141], 2.0, 2.04 (two acetate methyl groups), 1.02 (C10-CH_3), 0.7 (C13-CH_3), 0.93, 0.9 and 0.83 (other methyl protons).

Reaction of cholesta-3,5-dien-7-one (CCXVII) with performic acid.

To a mixture of 100 ml formic acid (98%) and 75 ml hydrogen peroxide (30%) in a three necked flask equipped with a thermometer and a motor-driven stirrer, the dienone (CCXVII)(3.0 g) was added and the reaction mixture was maintained at 40° by cooling in an ice bath. The stirring was continued for 3 hours. Then the reaction mixture was poured into ice cold water and extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution (5%), water and dried (anhydrous sodium sulphate). Removal of the solvent gave an oil (~3 g) which was chromatographed over silica gel (60 g) (each fraction of 20 ml was taken). Elution with light petroleum, pet.ether-ether (5:1) (fractions 1-10) gave no organic substance. Elution with pet.ether-ether (4:1) (fractions 11-14) gave a solid which was recrystallized from light petroleum to give cholest-5-ene-3,7-dione (CCXXX), (0.9 g), m.p. 165°; (Found: C, 81.8; H, 10.2. $C_{27}H_{42}O_2$ requires: C, 81.4; H, 10.5%); νmax. 1705 (C=O),

1680 (C=C-$\overset{O}{\overset{\|}{C}}$-) and 1625 cm^{-1} (C=C); λmax. 242 nm (log ϵ 3.65); N.m.r. δ6.1s (1 proton; C6-$\underline{H}$, vinylic proton), 2.15 umc (4 protons, C2-$\underline{H}_2$ and C4-$\underline{H}_2$), 1.2 (C10-Me), 0.71 (C13-Me), 0.95 and 0.85 (other methyl signals).

Elution with pet.ether-ether (3:1) (fraction 15-20) gave a solid which was crystallized from light petroleum to give 3α,4α-epoxycholest-5-en-7-one (CCXVIII), m.p. 136°; M^+ 398 ($C_{27}H_{42}O_2$); (Found: C, 81.8; H, 10.2. $C_{27}H_{42}O_2$ requires: C, 81.4; H, 10.5%); λmax. 241 nm (log ϵ 3.46); νmax. 1680 (C=C-C=O), 1638 (C=C), 870 and 775 cm^{-1} (epoxide ring); δ (100 MHz) 5.95s (C6-$\underline{H}$), 3.38m (C3β-$\underline{H}$ and C4β-$\underline{H}$; $W_{\frac{1}{2}}$ = 5.0 Hz), 1.08 (C10-CH_3), 0.7 (C13-CH_3), 0.82, 0.9 and 0.93 (other methyl protons).

Elution with pet.ether-ether (2:1) (fractions 21-30) gave another solid (homogeneous by t.l.c.) which was recrystallized from light petroleum ether mixture to give 3α-formyloxy-4β-hydroxycholest-5-en-7-one (CCXXVII) (0.75 g), m.p. 162°; λ max. 242 nm (log ϵ 3.48); ν max. 1735 ($-\overset{O}{\overset{\|}{C}}-O-$), 1685 ($-\overset{O}{\overset{\|}{C}}-C=C-$), 1620 (C=C), 3455 (OH), 1185 (formate ester), 1075 and 1020 cm^{-1} (C-O-); (Found: C, 75.9; H, 9.5. $C_{28}H_{44}O_4$ requires: C, 75.6; H, 9.9%); δ (100 MHz): 8.1s (1 proton, -O-$\overset{O}{\overset{\|}{C}}$-$\underline{H}$), 5.8s (1 proton, C6-$\underline{H}$, vinylic proton), 5.26br (1 proton, $W_{\frac{1}{2}}$ = 8 Hz, $\underline{H}$C3-O-$\overset{O}{\overset{\|}{C}}$-, equatorial, β-oriented), 4.6br,s (C4-O$\underline{H}$, disappeared on addition of D_2O), 4.2d like (1 proton, J = 3.5 Hz, $W_{\frac{1}{2}}$ = 5 Hz, $\underline{H}$-C4-OH,

equatorial, α-oriented), 1.4s (3 protons, C10-Me), 0.7s (3 protons, C13-Me), 0.93 and 0.85 (other methyl signals).

Further elution with ether (fractions 31-35) gave another solid (homogeneous by t.l.c.) which was recrystallized from ether and light petroleum mixture to give 3α,4β-dihydroxycholest-5-en-7-one (CCXIX) (150 mg), m.p. 205°; M^+ 416 ($C_{27}H_{44}O_3$); (Found: C, 78.02; H, 10.3. $C_{27}H_{44}O_3$ requires: C, 77.8; H, 10.5%); λ max. 244 nm (log ϵ 3.36); νmax. 3360 (-OH), 1680 (C=C-C=O), 1640(sh) (C=C), 1075, 1022 and 1015 cm^{-1} (C-O); δ (100 MHz): 5.75 (C6-$\underline{H}$), 4.05 (C3-$\underline{H}$ and C4-$\underline{H}$; $W_{\frac{1}{2}}$ = 6 Hz)[141], 1.34 (C10-CH_3) 0.68 (C13-CH_3), 0.83, 0.9 and 0.94 (other methyl protons).

REFERENCES

REFERENCES

1. A.E. Finholt, A.C. Bond, Jr., and H.I. Schlesinger, J. Am. Chem. Soc., 69, 1199 (1947).

2. E. Wiberg, H. Graf, M. Schmidt and R. UsonLacal, Z. Naturforsch., 76, 578 (1952).

3. E. Wiberg and W. Gosel, Z. Naturforsch, 11b, 485 (1956).

4. H.C. Brown and N.M. Yoon, J. Am. Chem. Soc., 88, 1464 (1966).

5. E. Wiberg and M. Schmidt, Z. Naturforsch, 6b, 333 (1951).

6. E. Wiberg and M. Schmidt, Z. Naturforsch, 6b, 460 (1951).

7. E.C. Ashby and J. Prather, J. Am. Chem. Soc., 88, 729 (1966).

8. U.E. Diner, H.A. Davis and R.K. Brown, Can. J. Chem., 45, 207 (1967).

9. E.L. Eliel, Record Chem. Progr. 22, 129 (1961).

10. E.L. Eliel and T.J. Brett, J. Org. Chem., 28, 1923 (1963).

11. E. Wiberg and M. Schmidt, Z. Naturforsch, 6b, 459 (1951).

12. E. Wiberg and M. Schmidt, Z. Naturforsch, 6b, 458 (1951).

13. G.G. Evans, J.K. Kennedy, Jr., and F.P. Del Greco, J. Inorg. Nucl. Chem., 4, 40 (1957).

14. G.G. Evans and F.P. Del Greco, J. Inorg. Nucl. Chem., 4, 48 (1957).

15. S.M. Arkhipov and V.I. Mikheeva, Zh. Neorg. Khim., 11, 2006 (1966); Chem. Abstr., 66, 2417, 25655t (1967).

16. T. Hayashi and T. Ishida, Bull. Univ. Osaka Project. Ser, A7, 55 (1959); Chem. Abstr., 54, 7398 (1960).

17. E.L. Eliel, V.G. Badding, and M.N. Rerick, J. Am. Chem. Soc., 84, 2371 (1962).

18. P.C. Maybury and W.S. Koski, J. Chem. Phys., 21, 742 (1953).

19. J.C. Warf and W. Feitknecht, Helv. Chim. Acta, 33, 613 (1950).

20. E.C. Ashby, Adv. in Inorganic Chemistry and Radiochemistry, Vol. 8, Academic Press, New York, 1966, p. 283-335.

21. W.L. Tweedie and B.G. Barron, J. Org. Chem., 25, 2023 (1960).

22. G.A. Olah, J. Am. Chem. Soc., 81, 3165 (1959).

23. G.W. Schaeffer, J.S. Roscoe, and A.C. Stewart, ibid., 78, 729 (1956).

24. A.C. Stewart and G.W. Schaeffer, J. Inorg. Nucl. Chem. 3, 194 (1956).

25. Y. Takegame, T. Ueno, and T. Fugii, Bull. Chem. Soc. Japan, 38, 1279 (1965).

26. P.T. Lansbury and R. Thedford, J. Org. Chem., 27, 2383 (1962).

27. P.T. Lansbury, J. Am. Chem. Soc., 83, 429 (1961).

28. P.T. Lansbury, J.R. Rogozinski, and F.L. Coblentz, J. Org. Chem., 26, 2277 (1961).

29. P.T. Lansbury and J.B. Peterson, J. Am. Chem. Soc., 85, 2236 (1963).

30. H.C. Brown and C.J. Shoaf, J. Am. Chem. Soc., 86, 1079 (1964).

31. H. Haubenstock and E.L. Eliel, ibid., 84, 2363 (1962).

32. H.I. Schlesinger, H.C. Brown, and E.K. Hyde, ibid., 75, 209 (1953).

33. H.C. Brown and B.C. Subba Rao, ibid., 78, 2582 (1956).

34. W.M. Olsen and R.T. Sanderson, J. Inorg. Nucl. Chem., 7, 228 (1958).

35. H.I. Schlesinger, H.C. Brown, H.R. Hockstra, and L.R. Rapp, J. Am. Chem. Soc., 75, 199 (1953).

36. H.C. Brown and P.A. Tierney, ibid., 80, 1552 (1958).

37. H.C. Brown and B.C. Subba Rao, ibid., 82, 681 (1960).

38. G.R. Pettit and T.R. Kashiri, J. Org. Chem., 26, 4557 (1961).

39. H.C. Brown, E.J. Meed, and B.C. Subba Rao, J. Am. Chem. Soc., 77, 6209 (1955).

40. J. Kollonitsch, O. Fuchs, and V. Gabor, Nature, 173, 125 (1954).

41. J. Kollonitsch, O. Fuchs, and V. Gabor, ibid., 175, 384 (1955).

42. B.C. Subba Rao, Current Sci., 30, 218 (1961).

43. T. Goto and Y. Kishi, Nippon Kagaku Zasshi, 83, 1135 (1962); Chem. Abstr., 58, 14059 (1963).

44. T. Goto and Y. Kishi, Tetrahedron Letters, 513 (1961).

45. B.C. Subba Rao and G.P. Thakar, J. Sci. Ind. Res., 20B, 317 (1961).

46. D. Goerring, French Pat. 1, 318, 419 (1963); Chem. Abstr., 59, 3854 (1963).

47a. H.C. Brown, E.J. Meed, and P.A. Tierney, J. Am. Chem. Soc., 79, 5400 (1957).

b. H.C. Brown, E.J. Meed, and C.J. Shoaf, ibid., 78, 3616 (1956).

48. H. Haubenstock and E.L. Eliel, ibid., 84, 2368 (1962).

49. H.M. Doukas and T.D. Fontaine, J. Am. Chem. Soc., 73, 5917 (1951); 75, 5355 (1953).

50. E.L. Eliel, Record Chem. Frogr., 23, 129 (1961).

51. E.L. Eliel and M.N. Rerik, J. Org. Chem., 23, 1088 (1958).

52. E.L. Eliel, V.G. Badding, and M.N. Rerik, J. Am. Chem. Soc., 84, 2371 (1962).

53. B.E. Leggetter and R.K. Brown, Can. J. Chem., 42, 990 (1964).

54. W. Ruske and I. Hartmann, J. Prakt. Chem., 18, 150 (1962).

55. B.E. Leggetter and R.K. Brown, Can. J. Chem., 43, 1030 (1965).

56. W.W. Zajac, Jr., B. Rhee, and R.K. Brown, ibid., 44, 1547 (1966).

57. P.C. Loewen, W.W. Zajac, Jr., and R.K. Brown, ibid., 47, 4059 (1969).

58. Syntex Corp. Netherlands Pat. App. 6, 405, 756; Chem. Abstr., 62, 10487 (1965).

59. G.R. Pettit and W.J. Bowyer, J. Org. Chem., 25, 84 (1960).

60. M.S. Ahmad and G.A.S. Ansari, Ind. J. Chem., 10, 1052 (1972).

61. M.S. Ahmad and S.C. Logani, Aust. J. Chem., 24, 143 (1971).

62. M.S. Ahmad, Shafiullah and S.C. Logani, Aust. J. Chem., 21, 1909 (1968).

63. M.S. Ahmad, S.C. Logani and G.A.S. Ansari, Ind. J. Chem., 9, 1329 (1971).

64. M.S. Ahmad and R.P. Sharma, Aust. J. Chem., 21, 527 (1968).

65. G.A.S. Ansari, Ph.D. Thesis, A.M.U. Aligarh (1972).

66. C. Djerassi and T. Nakano, Chem. and Ind., 1385 (1960).

67. R.P. Holysz, J. Am. Chem. Soc., 75, 4432 (1953).

68. J.C. Jacqnesy and J. Levissales, Bull. Soc. Chim., France, 189 (1962).

69. J.C. Jacqnesy and J. Levissales, Bull. Soc. Chim. France, 1866 (1962).

70. E.J. Corey, J. Am. Chem. Soc., 75, 2301 (1953).

71. E.J. Corey, J. Am. Chem. Soc., 76, 175 (1954); E.J. Corey and R.A. Sneen, J. Am. Chem. Soc., 78, 6269 (1950).

72. R.N. Jones, D.A. Ramsay, F. Herling and Dobriner, J. Am. Chem. Soc., 74, 2828 (1952).

73. I.M. Heilbron, E.R.H. Jones and F.S. Spring, J. Chem. Soc., 801 (1937).

74. C. Djerassi, Jeanne Osiocki, R.R. and Bernhard Riniker, J. Am. Chem. Soc., 80, 1216 (1958).

75. C. Djerassi, N. Finch, R.C. Cookson and C.W. Bird, J. Am. Chem. Soc., 82, 5488 (1960).

76. I.M. Heilbron, H. Jackson, E.R.H. Jones and F.S. Spring, J. Chem. Soc., 102 (1938).

77. E.W. Warnhoff and Pactong NaNonggai, J. Org. Chem., 27, 1186 (1962).

78. R.B. Woodward and A.F. Clifford, J. Am. Chem. Soc., 63, 2727 (1941).

79. H.H. Inhoffen and G. Zuhlsdroff, Chem. Ber., 74, 604 (1941).

80. R.L. Clarke, J. Am. Chem. Soc., 84, 467 (1962).

81. C. Djerassi and C.R. Scholz, J. Am. Chem. Soc., 70, 1911(1948).

82. A.S. Dreiding and A. Voltman, J. Am. Chem. Soc., 76, 537(1954).

83. A.L. Wilds and C. Djerassi, J. Am. Chem. Soc., 68, 1712 (1946).

84. C. Djerassi and C.R. Scholz, J. Am. Chem. Soc., 69, 2404 (1947)

85. H.H. Inhoffen and G. Stoeck, Ann. Chem., 563, 127 (1949).

86. H.H. Inhoffen, G. Koelling and P. Nehring, Chem. Ber., 85, 84 (1952).

87. C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki and Kaufmann, J. Am. Chem. Soc., 72, 4542 (1950).

88. F. Sondheimer and Y. Mazur, J. Am. Chem. Soc., 79, 2906 (1957).

89. A.M. Gold and E. Schwenk, J. Am. Chem. Soc., 80, 5683 (1958).

90. E. Caspi, P.K. Grover, N. Grover, E.J. Lynde and T. Nussbaumer, J. Chem. Soc., 1710 (1962).

91. E. Caspi and P.K. Grover, Steroids, 1, 39 (1963).

92. J. Libman and Y. Mazur, Chem. Comm., 14, 729 (1971).

93. J.R. Hanson, Tetrahedron Letters, 44, 4501 (1972).

94. J.R. Hanson, Chem. Comm., 1119 (1971).

95. K. Tsuda, K. Arima and R. Hayatsu, J. Am. Chem. Soc., 76, 2933 (1954).

96. P. Bladon, J. Chem. Soc., 2176 (1955).

97. J. Libman and Y. Mazur, Chem. Comm., 1146 (1971).

98. J. Libman and Y. Mazur, Chem. Comm., 14, 730 (1971).

99. R.B. Turner, J. Am. Chem. Soc., 72, 878 (1950).

100. A. Baeyer and V. Villiger, Chem. Ber., 32, 3625 (1899).

101. G. Wittig and G. Pieper, Chem. Ber., 73, 295 (1940).

102. W. Treibs, Chem. Ber., 72, 1194 (1939).

103. J. Boeseken, Proc. Acad. Sci. Amsterdam, 33, 134 (1930); (Chem. Abstr., 24, 3806, 1930).

104. R. Criegee, Annalen, 560, 127 (1948).

105. S.L. Friess, J. Am. Chem. Soc., 71, 2571 (1949).

106. W. Von E. Doering and E. Dorfman, J. Am. Chem. Soc., 75, 5595 (1953).

107. J.C. Robertson and A. Swelim, Tetrahedron Letters, 2871 (1967).

108. S.L. Friess and A.H. Soloway, J. Am. Chem. Soc., 73, 3968 (1951).

109. M.F. Hawthorne and W.D. Emmons, J. Am. Chem. Soc., 80, 6398 (1958).

110. Y. Yukawa and T. Yokoyama, Mem. Inst. Sci. Ind. Research Osaka Univ., 9, 180, 1952 (Chem. Abstr., 49, 5370, 1955).

111. R.R. Sauers, J. Am. Chem. Soc., 81, 925 (1958).

112. G.W. Ellis and J.A. Gardner, Biochem. J., 12, 72 (1918).

113. G.A. Gardner and W. Godden, ibid., 7, 588 (1913).

114. D. Rosenthal, A.O. Niedermeyer and J. Fried, J. Org. Chem., 30, 510 (1965).

115. J.S.E. Holker, W.R. Jones and P.J. Ramm, J. Chem. Soc., 357 (1969).

116. G.J. Fonken and H.M. Miles, J. Org. Chem., 28, 2432 (1963).

117. H. Heusser, A. Segre and A. Plattner, Helv. Chim. Acta., 31, 1183 (1948).

118. E.S. Rothman, T. Perlstein and M.E. Wall, J. Org. Chem., 25, 1966 (1960).

119. P. Bladon and W. McMeekin, J. Chem. Soc., 3504 (1961).

120. N.L. Wendler, D. Taub and H.L. Slates, J. Am. Chem. Soc., 77, 3559 (1955).

121. A. Lardon, J. Schmidlin, A. Wettstein and T. Reichstein, Helv. Chim. Acta, 40, 662 (1957).

122. W.W. Westerfeld, J. Biol. Chem., 143, 177 (1942).

123. N. Prilejaeff, Bull. Soc. Chim. France, 41, 687 (1927).

124. J. Boeseken and A.L. Soesman, Rec. Trav. Chim., 52, 874 (1933).

125. H.M. Walton, J. Org. Chem., 22, 1161 (1957).

126. G.B. Payne and P.H. Williams, ibid., 24, 284 (1959).

127. J.T. Pinhey and K. Schaffner, Aust. J. Chem., 21, 1873 (1968).

128. M. Gorodetsky, M. Danieli and Y. Mazur, J. Org. Chem., 32, 760 (1967).

129. J.T. Pinhey and K. Schaffner, Tetrahedron Letters., 601(1965).

130. E. Caspi and Y. Schimizu, J. Org. Chem., 30, 223 (1955).

131. E. Caspi and S.N. Balasubrahmanyam, J. Org. Chem., 3383(1963).

132. M.S. Ahmad, Shafiullah, M. Mushfiq and M. Asif, Ind. J. Chem., 8, 1062 (1970).

133. M.S. Ahmad, A.H. Siddiqi and Shafiullah, Ind. J. Chem., 8, 786 (1970).

134. M.S. Ahmad, Shafiullah and M. Mushfiq, Aust. J. Chem., 27, 2673 (1974).

135. Kirk, D.N. Kirk, and Hartshorn, M.P., "Steroid Reaction Mechanism", Elsevier, Amsterdam (1968).

136. Ph.D. Thesis of N.K. Pillai, Aligarh Muslim University, Aligarh (1973).

137. L.F. Fieser, J. Am. Chem. Soc., 75, 4386 (1953).

138. L.F. Fieser, J. Am. Chem. Soc., 75, 4291 (1953).

139. C.R. Narayanan and K.N. Ayer, J. Org. Chem., 30, 1734 (1965).

140. L. Tokes, G. Jones and C. Djerassi, J. Am. Chem. Soc., 90, 5465 (1968).

141. N.S. Bhacca, D.H. Williams, 'Application of N.M.R. Spectroscopy in Organic Chemistry'. Holden-Day, Inc. San Francisco (1964).

142. E. Schwenk and B. Whitman, J. Am. Chem. Soc., 59, 948 (1937).

143. L.J. Bellamy, "The Infra-red spectra of complex molecules", John Wiley and Sons., Inc. New York, 1958.

144. S. Akagi and K. Tsuda, Chem. Pharm. Bull. (Japan), 9, 464 (1967).

145. H. Budzikiewicz, C. Djerassi and D.H. Williams, "Interpretation of mass spectra of Organic compounds", Holden-Day, San Francisco (1967).

146. H. Budzikiewicz, C. Djerassi and D.H. Williams, "Interpretation of Mass spectra of organic compounds", Holden-Day, San Francisco (1964).

147. H. Budzikiewicz and C. Djerassi, J. Am. Chem. Soc., 84, 1430 (1962).

148. L.F. Fieser and S. Rajagopalan, J. Am. Chem. Soc., 71, 3938 (1949).

149. L.F. Fieser and M. Fieser, "Steroids", Reinhold Publishing Corporation, New York (1959).

150. C.E. Anagnostopoulos and L.F. Fieser, J. Am. Chem. Soc., 76, 532 (1954).

151. R.M. Dodson and B. Riegel, J. Org. Chem., 13, 424 (1948).

152. W.G. Dauben and G.J. Fonken, J. Am. Chem. Soc., 78, 4736 (1956).

153. Q.R. Petersen and C.T. Chen, J. Am. Chem. Soc., 77, 2557 (1955).

154. PL. A. Plattner and W. Lang, Helv. Chim. Acta, 27, 1872 (1944).

155. D.H.R. Barton and W.J. Rosenfelder, J. Chem. Soc., 2381 (1951).

156. D.H.R. Barton and W.J. Rosenfelder, J. Chem. Soc., 2459 (1949).